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(71) Applicants: **REGENTS OF THE UNIVERSITY OF MICHIGAN** [US/US]; C/o Innovation Partnerships, 1600 Huron Parkway, 2nd Floor, Ann Arbor, MI 48109 (US). **ONCOPIA THERAPEUTICS, INC. D/B/A/PROTEOVANT THERAPEUTICS, INC.** [US/US]; 151 W 42nd St. 15th Floor, New York, NY 10036 (US).

(72) Inventors: **XU, Gouzhang**; 151 W. 42nd St. 15th Floor, New York, NY 10036 (US). **CHEN, Zhixiang**; 1600 Huron Pkwy, Ann Arbor, MI 48109-2800 (US). **REJ, Rohan**; 3655 Greenbrier Blvd, Apartment 139b, Ann Arbor, MI 48105 (US). **ACHARYYA, Ranjan, Kumar**; 1803 Willowtree Lane, 1b6, Ann Arbor, MI 48105 (US). **WU, Dimin**; 1877 Lake Lila Ln Apt B4, Ann Arbor, MI 48105 (US). **WANG, Mingliang**; 1427 Natalie Ln, Apt 108, Ann Arbor, MI 48105-2918 (US). **HU, Biao**; 1636 Chapleau Drive, Ann Arbor, MI 48103 (US). **LU, Jianfeng**; 4982 S. Ridgeside Cir, Ann Arbor, MI 48105 (US). **LI, Zhenwu**; 151 W. 42nd St. 15th Floor, New York, NY 10036 (US). **PRIESTLEY, E., Scott**; 151 W. 42nd St. 15th Floor, New York, NY 10036 (US). **WANG, Shaomeng**; 3336 Stirling Ct., Superior Township, MI 48198 (US).

(74) Agent: **NAPOLI, James, J.**; Marshall, Gerstein & Borun LLP, 233 S. Wacker Drive, 6300 Willis Tower, Chicago, IL 60606-6357 (US).

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(54) Title: TETRAHYDRONAPHTHALENE DERIVATIVES AS ESTROGEN RECEPTOR DEGRADERS

(57) Abstract: Described herein are compounds of Formula I and their pharmaceutically acceptable salts, solvates, or stereoisomers, as well as their uses (e.g., as estrogen receptor degraders).

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TETRAHYDRONAPHTHALENE DERIVATIVES AS ESTROGEN RECEPTOR DEGRADERS

RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/388,300, filed July 12, 2022; U.S. Provisional Application No. 63/408,744, filed September 21, 2022; U.S. Provisional Application No. 63/427,277, filed November 22, 2022; and U.S. Provisional Application No. 63/460,734, filed April 20, 2023; the contents of each of which are incorporated herein by reference in their entireties.

BACKGROUND

[0002] Estrogen receptors (ERs) belong to the steroid/nuclear receptor superfamily involved in the regulation of eukaryotic gene expression, cellular proliferation, and differentiation in target tissues. ERs are in two forms: the estrogen receptor alpha (ERα) and the estrogen receptor beta (ERβ) respectively encoded by the ESR1 and the ESR2 genes. ERα and ERβ are ligand-activated transcription factors which are activated by the hormone estrogen (17β-estradiol). In the absence of hormone, ERs are largely located in the cytosol of the cell. When the hormone estrogen binds to ERs, ERs migrate from the cytosol to the nucleus of the cell, form dimers and then bind to specific genomic sequences called Estrogen Response Elements (ERE). The DNA/ER complex interacts with co-regulators to modulate the transcription of target genes. ERα is mainly expressed in reproductive tissues such as uterus, ovary, breast, bone, and white adipose tissue. It is well known that deregulation of ER signaling, specifically through ERα, results in uncontrolled cellular proliferation which eventually results into cancer. ER+ breast cancer accounts for approximately 75% of all breast cancers diagnosed, as well as some ovarian and endometrial cancers.

[0003] Current therapy for ER+ breast cancer including agents that inhibit the ER activity through direct binding to the ligand binding domain of the receptor (e.g., tamoxifen); blocking the synthesis of estrogen (e.g., aromatase inhibitor such as anastrozole and letrozole); or inducing the degradation of ER. Selective estrogen receptor degraders (SERD) are small molecules that target ERα for proteasome-dependent degradation. Fulvestrant is the only SERD that has been approved for the treatment of postmenopausal women with advanced ER+ breast cancer with standard endocrine therapies. Because it has poor solubility and is not orally bioavailable, fulvestrant is administered clinically by a monthly intramuscular injection. To address the shortcomings of

fulvestrant, oral bioavailable SERDs are being developed. However, the SERDs are only able to achieve partial degradation of the ER protein despite they are typically potent and effective in inducing degradation of ER protein in ER+ breast cancer cells.

[0004] It is believed that ERα degradation may occur when both ERα and a ubiquitin ligase (e.g., cereblon E3 ligase (CRBN)) are bound and brought into close proximity for ubiquitination and subsequent degradation by proteasomes. A new approach would be to utilize the naturally occurring cellular ubiquitin-mediated degradation to develop a completely new class of therapeutics for the treatment of ER+ metastatic breast cancer with nearly complete degradation of ER protein.

SUMMARY

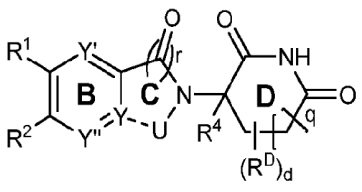
[0005] In certain aspects, the present disclosure provides compounds of Formula **I**:

T-L-C (**I**),

and pharmaceutically acceptable salts, solvates, or stereoisomers thereof,

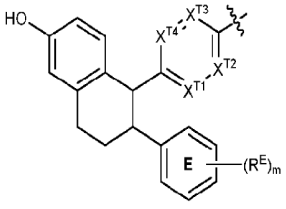
wherein:

C is of Formula **I'-1**



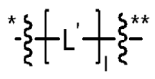
(**I'-1**),

T is of Formula **I-2**:



(**I-2**), and

L is of Formula **I'-3**:



(**I'-3**),

wherein each of the variables in Formulae **I**, **I'-1**, **I-2**, and **I'-3**, is described, embodied, and exemplified herein.

[0006] In certain aspects, the present disclosure provides pharmaceutical compositions comprising a compound disclosed herein, and a pharmaceutically acceptable excipient.

[0007] In certain aspects, the present disclosure provides methods of degrading an estrogen receptor in a subject, comprising administering to the subject a compound disclosed herein.

[0008] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for degrading an estrogen receptor in a subject.

[0009] In certain aspects, the present disclsoure provides compounds disclosed herein for use in degrading an estrogen receptor in a subject.

[0010] In certain aspects, the present disclosure provides methods of treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject a compound disclosed herein (e.g., in a therapeutically effective amount).

[0011] In certain aspects, the present disclosure provides methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a compound disclosed herein (e.g., in a therapeutically effective amount).

[0012] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating or preventing a disease or disorder in a subject in need thereof.

[0013] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

[0014] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating or preventing a disease or disorder in a subject in need thereof.

In certain aspects, the present disclosure provides compounds disclosed herein for use in treating a disease or disorder in a subject in need thereof.

DETAILED DESCRIPTION

[0015] The present disclosure relates to compounds and methods of degrading an estrogen receptor comprising contacting the estrogen receptor with a therapeutically effective amount of an estrogen receptor degrader disclosed herein. The present disclosure also relates to methods of treating an estrogen receptor-mediated disease or condition in a subject in need thereof by

administering a therapeutically effective amount of an estrogen receptor degrader disclosed herein. The present disclosure further relates to methods of treating an estrogen receptor-mediated disease or condition in a subject in need thereof, comprising administering a pharmaceutical composition comprising a therapeutically effective amount of an estrogen receptor degrader disclosed herein.

Compounds of the Application

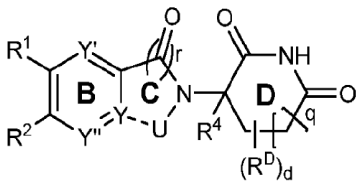
[0016] In one aspect, the present disclosure provides compounds of Formula **I**:

T-L-C (I),

and pharmaceutically acceptable salts, solvates, or stereoisomers thereof,

wherein:

C is of Formula **I'-1**



(I'-1),

wherein:

R^1 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

R^2 is *-Cy^2-, wherein * denotes attachment to **L**;

-Cy^2- is C_{3-12} carbocyclylene or 3- to 12-membered heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted with one or more R^u; or

R^1 and R^2, together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted C_{3-12} carbocycle or 5- to 16-membered heterocycle;

Y" is N or CR^3;

R^3 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-

membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; or

R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted 5- to 16-membered heterocycle;

provided that R^1 and R^2, and R^2 and R^3, do not both form Ring A attached to **L**;

Y' is N or $CR^{Y'}$;

$R^{Y'}$ is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

--- denotes an optional covalent bond between Y and U;

i) when the bond between Y and U is absent:

r is 0 or 1;

Y is N or CR^Y;

R^Y is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

U is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

ii) when the bond between Y and U is present:

r is 1;

Y is C;

U is $-CH_2-$, -C(=O)-, -(C=O)-N(R^U)-*, or -N=C(R^U)-*;

R^U is H or C_{1-6} alkyl optionally substituted with one or more R^u, and * denotes attachment to Ring B;

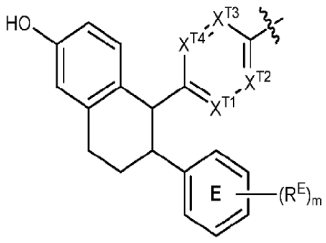
R^4 is hydrogen, deuterium, C_{1-6} haloalkyl, or C_{1-6} alkyl; and

each R^D is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

d is an integer from 0 to 4; and

q is an integer from 0 to 2,

T is of Formula **I-2**:



(**I-2**),

wherein:

each of X^{T1}, X^{T2}, X^{T3}, and X^{T4} is independently N or CR^T;

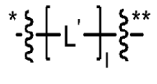
each occurrence of R^T is independently hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^cS(=O)R^a$, -$NR^cS(=O)_2OR^b$, -$NR^cS(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$OS(=O)_2R^a$, -$OS(=O)_2OR^b$, -$OS(=O)_2NR^cR^d$, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

each R^E is independently halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^cS(=O)R^a$, -$NR^cS(=O)_2OR^b$, -$NR^cS(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$OS(=O)_2R^a$, -$OS(=O)_2OR^b$, -$OS(=O)_2NR^cR^d$, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl,

alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

m is an integer selected from 0 to 5;

L is of Formula **I'-3**:



(I'-3),

wherein:

* denotes attachment to **T**, and ** denotes attachment to **C**;

each L' is independently C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{3-12} carbocyclylene, 3- to 12-membered heterocyclylene, C_{6-10} arylene, 5- to 10-membered heteroarylene, -C(=O)-, -C(=O)N(R^L)-, -C(=O)O-, -N(R^L)-, -O-, -S-, or -$S(=O)_2$-, wherein the alkylene, heteroalkylene, alkenylene, alkynylene, carbocyclylene, heterocyclylene, arylene, or heteroarylene is optionally substituted with one or more R^u;

each occurrence of R^L is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

l is an integer selected from 0 to 10,

wherein:

each R^u is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^cS(=O)R^a$, -$NR^cS(=O)_2OR^b$, -$NR^cS(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$OS(=O)_2R^a$, -$OS(=O)_2OR^b$, -$OS(=O)_2NR^cR^d$, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected

from oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl; or

two R^u, together with the one or more intervening atoms, form C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl;

each R^a is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl;

each R^b is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl; and

each R^c and R^d is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl; or

R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl,

wherein each occurrence of R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z; and

each R^z is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-memberred heterocyclyl.

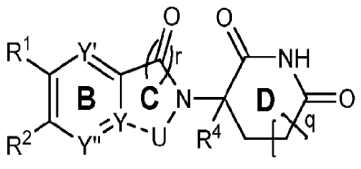
[0017] In certain aspects, the present disclosure provides compounds of Formula **I**:

T-L-C (I),

and pharmaceutically acceptable salts, solvates, or stereoisomers thereof,

wherein:

C is of Formula **I-1**



(I-1),

wherein:

R^1 is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^cS(=O)R^a$, -$NR^cS(=O)_2OR^b$, -$NR^cS(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$OS(=O)_2R^a$, -$OS(=O)_2OR^b$, -$OS(=O)_2NR^cR^d$, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl,

alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

R^2 is *-Cy^2-, wherein * denotes attachment to **L**;

-Cy^2- is C_{3-12} carbocyclylene or 3- to 12-membered heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted with one or more R^u; or

R^1 and R^2, together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted C_{3-12} carbocycle or 5- to 16-membered heterocycle;

Y" is N or CR^3;

R^3 is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^cS(=O)R^a$, -$NR^cS(=O)_2OR^b$, -$NR^cS(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$OS(=O)_2R^a$, -$OS(=O)_2OR^b$, -$OS(=O)_2NR^cR^d$, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; or

R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted 5- to 16-membered heterocycle;

provided that R^1 and R^2, and R^2 and R^3, do not both form Ring A attached to **L**;

Y' is N or $CR^{Y'}$;

$R^{Y'}$ is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

--- denotes an optional covalent bond between Y and U;

when the bond between Y and U is absent:

r is 0 or 1;

Y is N or CR^Y;

R^Y is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-

membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

U is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

when the bond between Y and U is present:

r is 1;

Y is C;

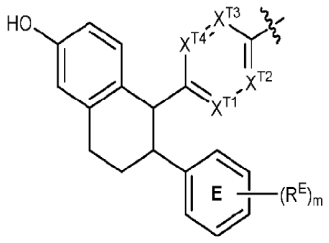
U is $-CH_2-$, -C(=O)-, -(C=O)-N(R^U)-*, or -N=C(R^U)-*;

R^U is H or C_{1-6} alkyl optionally substituted with one or more R^u, and * denotes attachment to Ring B;

R^4 is hydrogen, deuterium, C_{1-6} haloalkyl, or C_{1-6} alkyl; and

q is an integer from 0 to 2,

T is of Formula **I-2**:



(**I-2**),

wherein:

each of X^{T1}, X^{T2}, X^{T3}, and X^{T4} is independently N or CR^T;

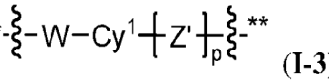
each occurrence of R^T is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

each R^E is independently halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, -

$NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

m is an integer selected from 0 to 5,

L is of Formula **I-3**:



(I-3),

wherein:

* denotes attachment to **T** and ** denotes attachment to **C**;

W is absent; or

W is C_{1-3} alkylene, -O-, $-NR^W$-, or -(C=O)- , wherein the alkylene is optionally substituted by one or more R^u;

Cy^1 is absent; or

Cy^1 is 6-membered heteroarylene, C_6 arylene, C_{3-12} carbocyclylene, or 3- to 12-membered heterocyclylene, wherein the arylene, heteroarylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u;

Z' is absent; or

each Z' is independently C_{1-3} alkylene, -O-, $-NR^W$-, -(C=O)-, C_{3-12} carbocyclylene, or 3- to 12-membered heterocyclylene, wherein the alkylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u;

R^W is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u; and

p is an integer selected from 0 to 8,

wherein:

each R^u is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, -

$NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl; or

two R^u, together with the one or more intervening atoms, form C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl;

each R^a is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl;

each R^b is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl; and

each R^c and R^d is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl; or

R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl,

wherein each occurrence of R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z; and

each R^z is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-memberred heterocyclyl.

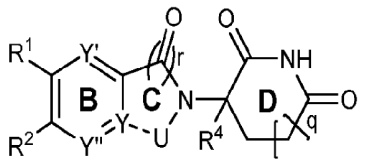
[0018] In certain aspects, the present disclosure provides compounds of Formula **I**:

T-L-C (I),

and pharmaceutically acceptable salts, solvates, or stereoisomers thereof,

wherein:

C is of Formula **I-1**



(I-1),

wherein:

--- denotes an optional covalent bond between Y and U;

R^1 is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-10} carbocyclyl, 3- to 10-membered heterocyclyl, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^cS(=O)R^a$, -$NR^cS(=O)_2OR^b$, -$NR^cS(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$OS(=O)_2R^a$, -$OS(=O)_2OR^b$, -$OS(=O)_2NR^cR^d$, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

R^2 is *-Cy^2-, wherein * denotes attachment to **L**;

-Cy^2- is 3- to 12-membered heterocyclylene, wherein the heterocyclylene is optionally substituted with one or more R^u; or

R^1 and R^2, together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is C_{3-10} carbocycle or 5- to 16-membered heterocycle optionally substituted with one or more R^i;

Y" is N or CR^3;

R^3 is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-10} carbocyclyl, 3- to 10-membered heterocyclyl, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^cS(=O)R^a$, -$NR^cS(=O)_2OR^b$, -$NR^cS(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$OS(=O)_2R^a$, -$OS(=O)_2OR^b$, -$OS(=O)_2NR^cR^d$, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; or

R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is 5- to 16-membered heterocycle optionally substituted with one or more R^i;

provided that R^1 and R^2, and R^2 and R^3, do not both form Ring A attached to **L**;

each R^i is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-10} carbocyclyl, 3- to 10-membered heterocyclyl, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^cS(=O)R^a$, -$NR^cS(=O)_2OR^b$, -$NR^cS(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$OS(=O)_2R^a$, -$OS(=O)_2OR^b$, -

$OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

Y' is N or $CR^{Y'}$;

$R^{Y'}$ is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

Y is N or CR^Y when the bond between Y and U is absent; or Y is C when the bond between Y and U is present;

R^Y is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

r is 0 or 1;

U is hydrogen or C_{1-6} alkyl when the bond between Y and U is absent; or

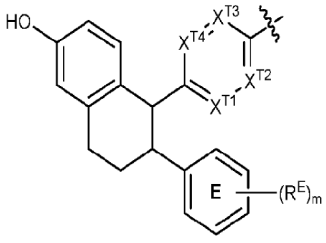
U is $-CH_2-$, -C(=O)-, $-(C=O)-N(R^U)-*$, or $-N=C(R^U)-*$ when the bond between Y and U is present;

R^U is H or C_{1-6} alkyl, and * denotes attachment to Ring B;

R^4 is hydrogen, deuterium, C_{1-6} haloalkyl, or C_{1-6} alkyl; and

q is an integer from 0 to 2;

T is of Formula **I-2**:



(**I-2**),

wherein:

each of X^{T1}, X^{T2}, X^{T3}, and X^{T4} is independently N or CR^T;

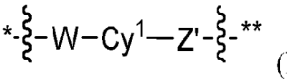
each occurrence of R^T is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-10} carbocyclyl, 3- to 10-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, -

$NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

each R^E is independently halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-14} aryl, 5- to 14-membered heteroaryl, C_{3-10} carbocyclyl, 3- to 10-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

m is an integer selected from 0 to 5,

L is of Formula **I-3**:



(**I-3**),

wherein:

W is absent; or

W is $-CH_2-$, -O-, $-NR^W-$, or -(C=O)-;

R^W is hydrogen or C_{1-6} alkyl;

* denotes attachment to **T** and ** denotes attachment to **C**;

Cy^1 is 6-membered heteroarylene, C_6 arylene, C_{3-12} carbocyclylene, or 3- to 12-membered heterocyclylene, wherein the arylene, heteroarylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u;

Z' is absent; or

Z' is $-(C(=O))_p-(O)_{p'}-(C_{1-6}$ alkylene$)_u-($3- to 6-membered heterocyclylene$)_v-(C(=O))_p-(C_{1-6}$ alkylene$)_u-($3- to 6-membered heterocyclylene$)_v-(C(=O))_p$, wherein the alkylene or heterocyclylene is optionally substituted by one or more R^u;

each occurrence of p, p', and u is independently 0 or 1; and

each v is an integer independently selected from 0 to 3,

wherein:

each R^u is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-10} carbocyclyl, 3- to 10-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl; or

two R^u, together with the one or more intervening atoms, form C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-10} carbocyclyl or 3- to 10-membered heterocyclyl;

each R^a is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3- to 10-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl;

each R^b is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3- to 10-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl; and

each R^c and R^d is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3- to 10-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl; or

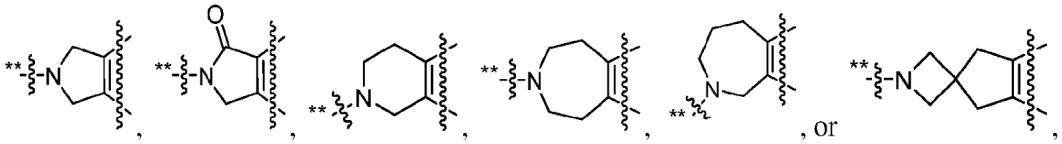
R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 10-membered heterocyclyl,

wherein each of R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z; and

each R^z is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-memberred heterocyclyl.

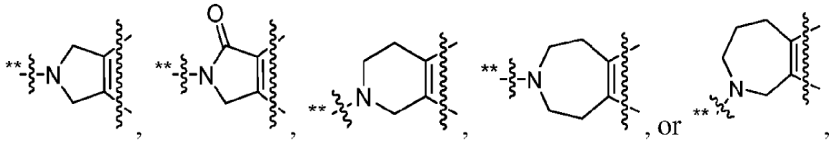
[0019] In certain embodiments, when the bond between Y and U is present, U is $-CH_2-$ or -C(=O)-, and r is 1, then either R^1 and R^2, or R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**.

[0020] In certain embodiments, when the bond between Y and U is present, U is $-CH_2-$ or -C(=O)-, and r is 1, then Ring A is not



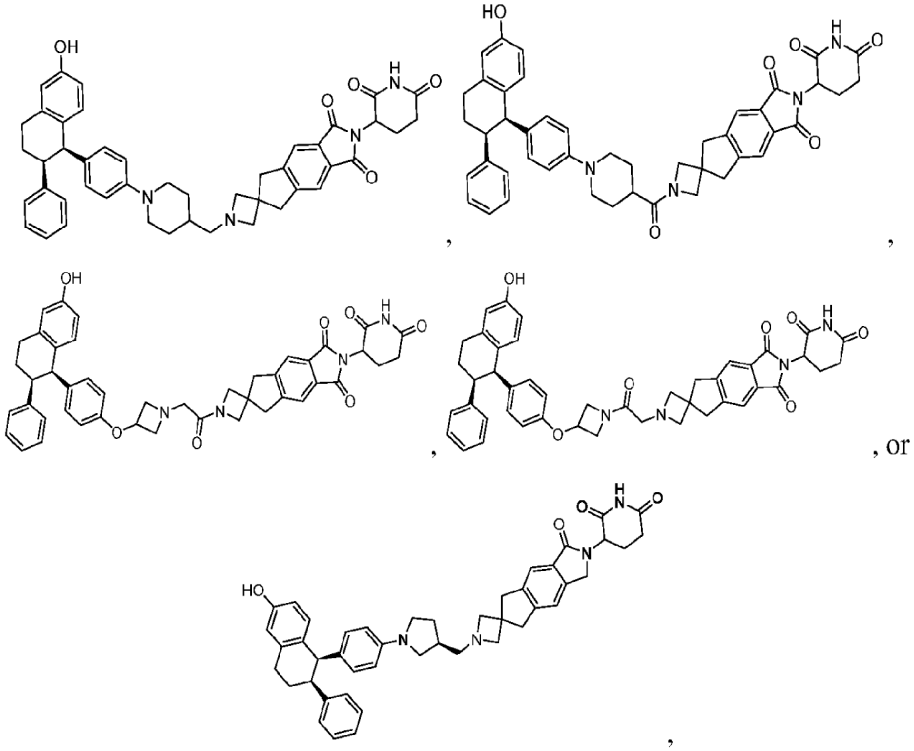
wherein ** denotes attachment to **L**.

[0021] In certain embodiments, when the bond between Y and U is present, U is $-CH_2-$ or -C(=O)-, and r is 1, then Ring A is not



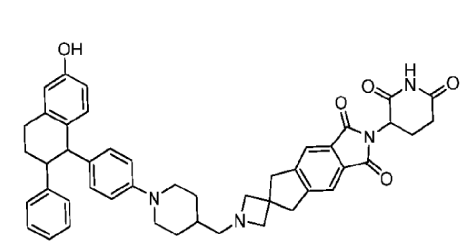
wherein ** denotes attachment to **L**.

[0022] In certain embodiments, the compound is not



or a pharmaceutically acceptable salt or stereoisomer thereof.

[0023] In certain embodiments, the compound is not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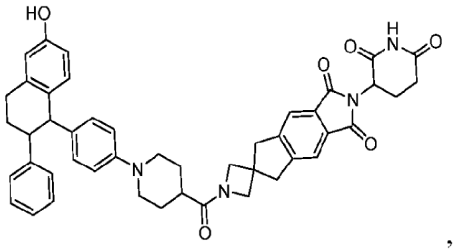
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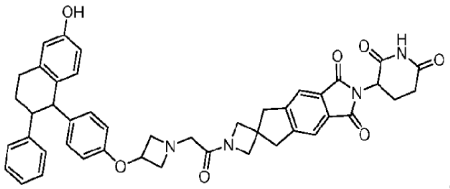
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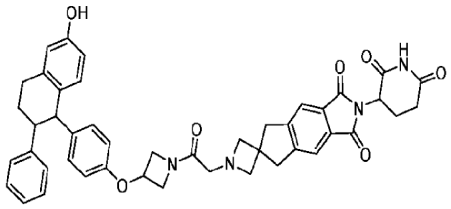
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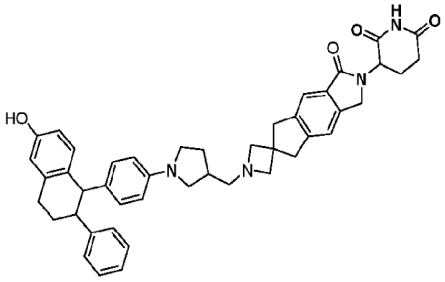
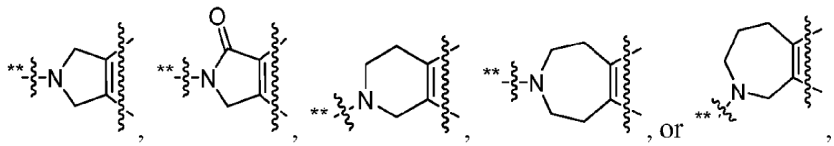

,

or a pharmaceutically acceptable salt thereof.

[0024] In certain embodiments,

1) when the bond between Y and U is present, U is $-CH_2-$ or $-C(=O)-$, and r is 1, then i) either R^1 and R^2, or R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**; and/or ii) Ring A is not


, or

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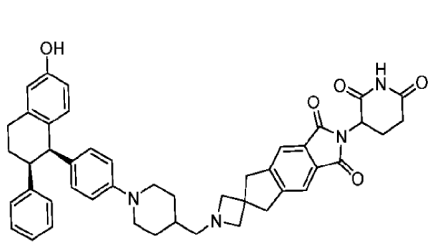
wherein ** denotes attachment to **L**, and/or

2) the compound is not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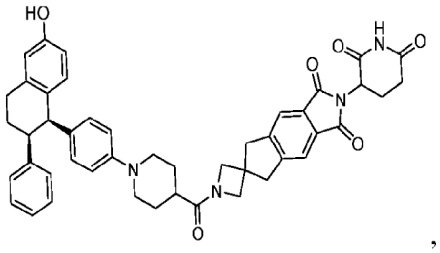
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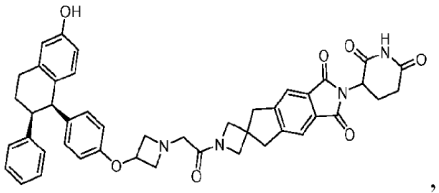
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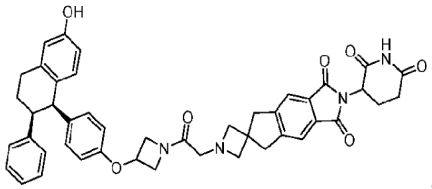
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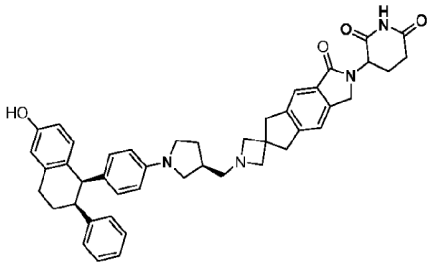
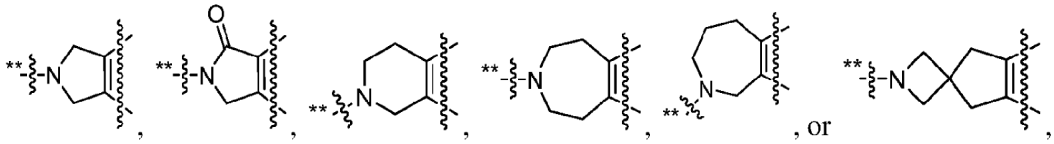

,

or a pharmaceutically acceptable salt or stereoisomer thereof.

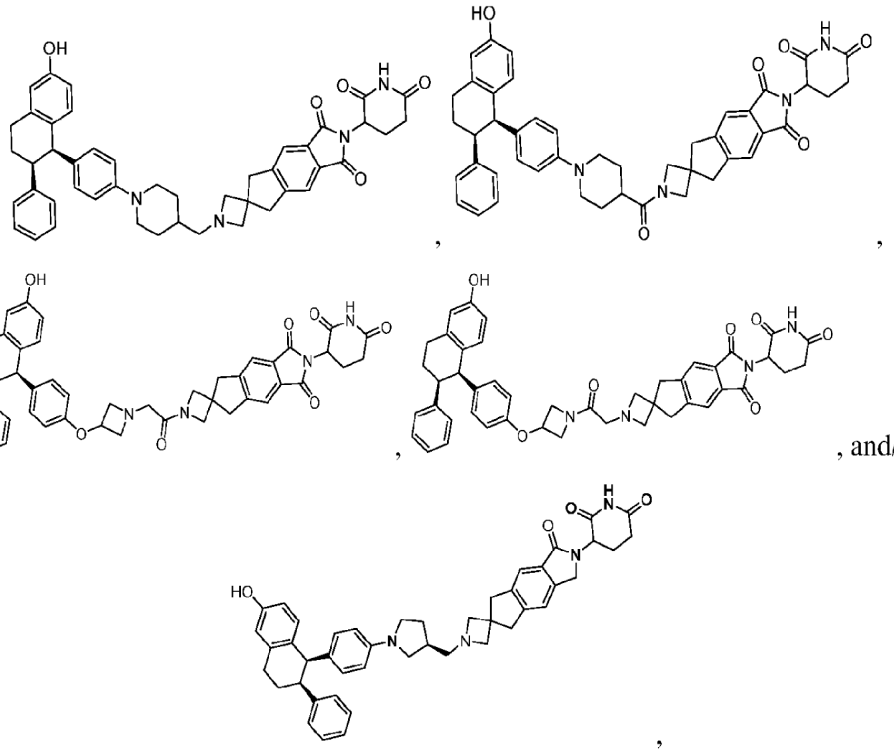
[0025] In certain embodiments,

1) when the bond between Y and U is present, U is $-CH_2-$ or $-C(=O)-$, and r is 1, then i) either R^1 and R^2, or R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**; and/or ii) Ring A is not



wherein ** denotes attachment to **L**, and/or

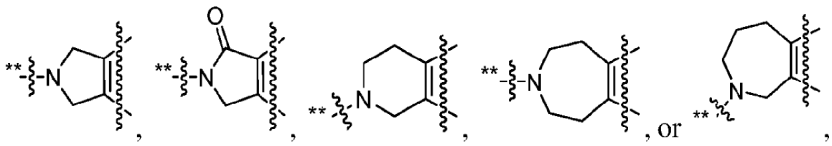
2) the compound is not



or a pharmaceutically acceptable salt or stereoisomer thereof.

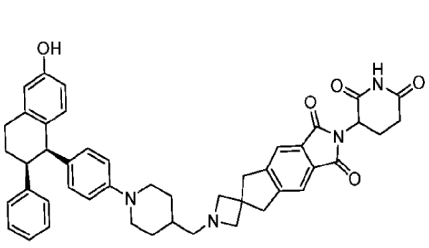
[0026] In certain embodiments,

1) when the bond between Y and U is present, U is -CH_2- or -C(=O)-, and r is 1, then i) either R^1 and R^2, or R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**; and/or ii) Ring A is not



wherein ** denotes attachment to **L**, and/or

2) the compound is not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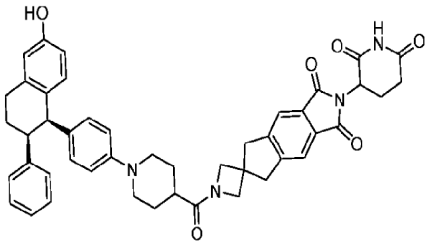
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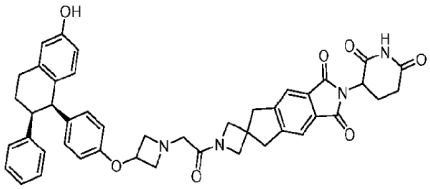
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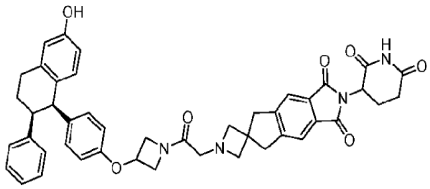
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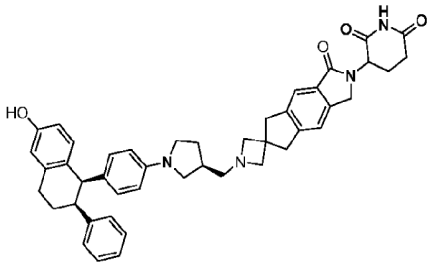
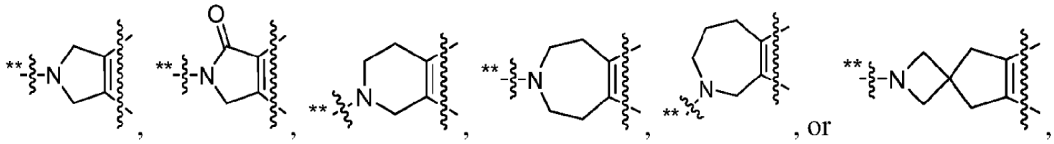

,

or a pharmaceutically acceptable salt or stereoisomer thereof.

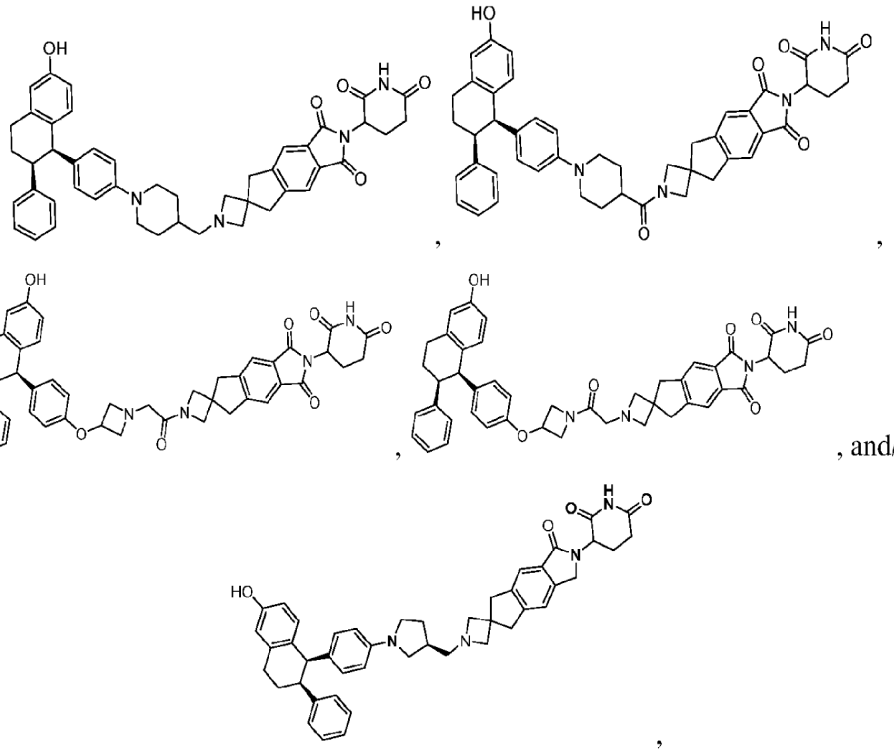
[0027] In certain embodiments,

1) when the bond between Y and U is present, U is $-CH_2-$ or $-C(=O)-$, and r is 1, then i) either R^1 and R^2, or R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**; and/or ii) Ring A is not



wherein ** denotes attachment to **L**, and/or

2) the compound is not



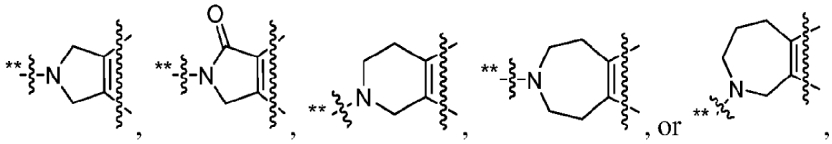
, and/or

,

or a pharmaceutically acceptable salt or stereoisomer thereof.

[0028] In certain embodiments,

1) when the bond between Y and U is present, U is $-CH_2-$ or $-C(=O)-$, and r is 1, then i) either R^1 and R^2, or R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**; and/or ii) Ring A is not



, or

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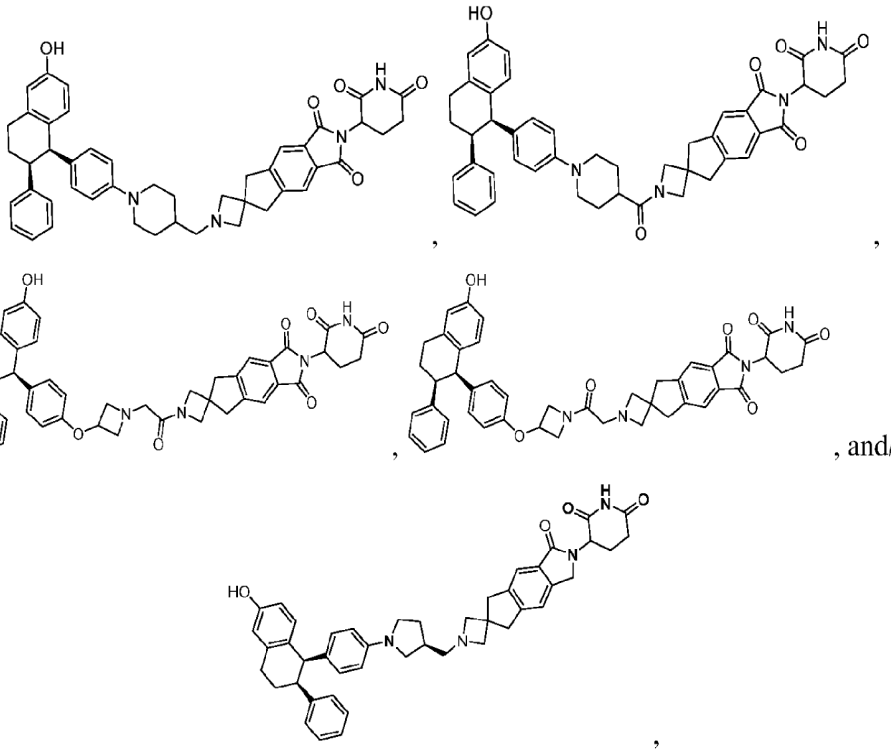
wherein ** denotes attachment to **L**, and/or

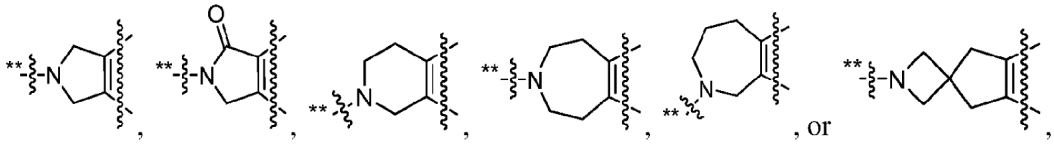
2) the compound is not



or a pharmaceutically acceptable salt or stereoisomer thereof.

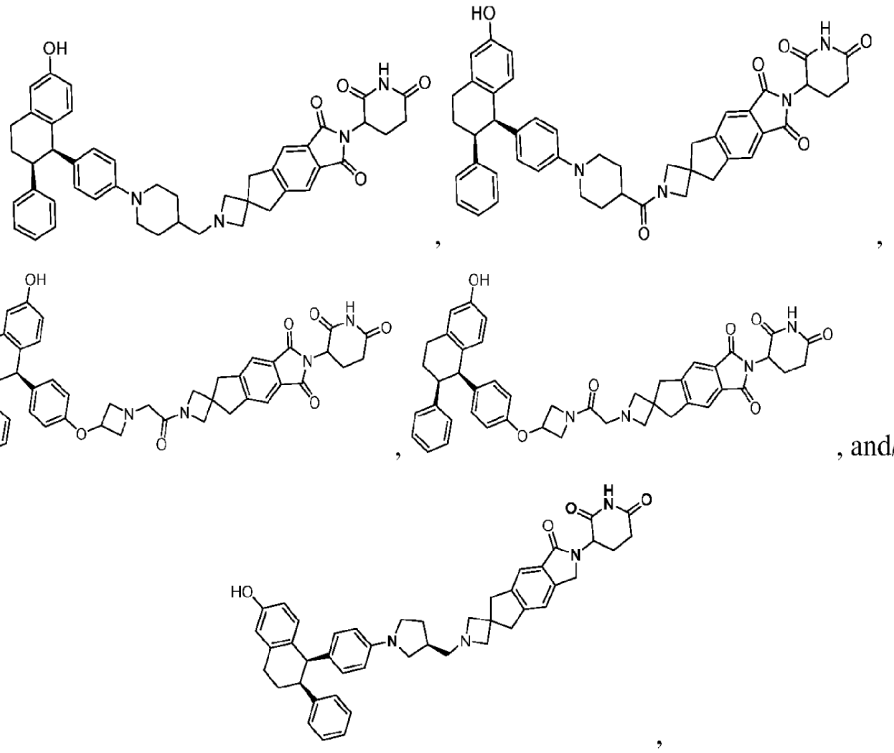
[0029] In certain embodiments,

1) when the bond between Y and U is present, U is $-CH_2-$ or $-C(=O)-$, and r is 1, then i) either R^1 and R^2, or R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**; and/or ii) Ring A is not



wherein ** denotes attachment to **L**, and/or

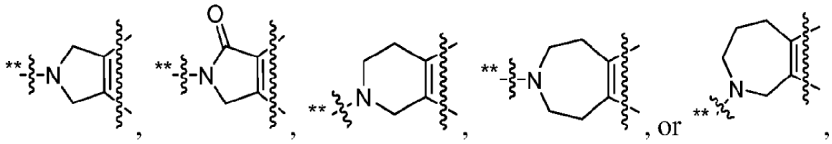
2) the compound is not



or a pharmaceutically acceptable salt or stereoisomer thereof.

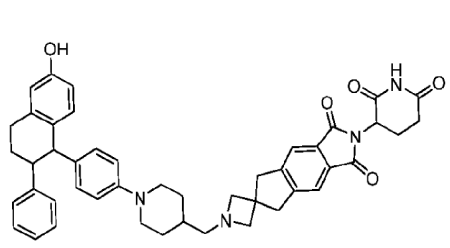
[0030] In certain embodiments,

1) when the bond between Y and U is present, U is -CH_2- or -C(=O)-, and r is 1, then i) either R^1 and R^2, or R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**; and/or ii) Ring A is not



wherein ** denotes attachment to **L**, and/or

2) the compound is not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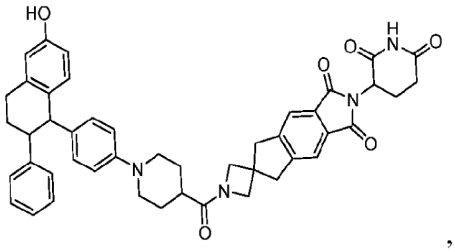
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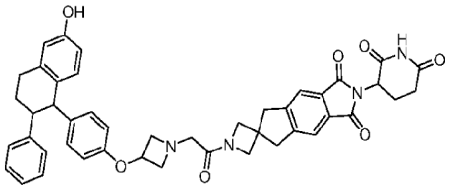
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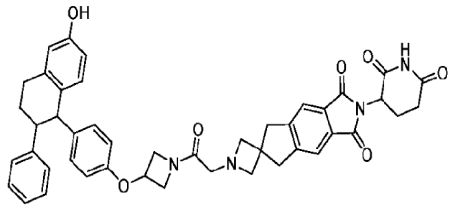
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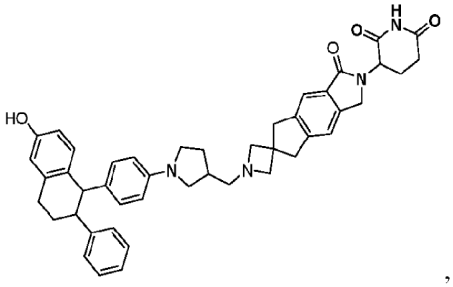
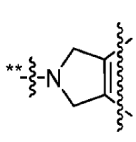

,

or a pharmaceutically acceptable salt or stereoisomer thereof.

[0031] In certain embodiments,

1) when the bond between Y and U is present, U is $-CH_2-$ or $-C(=O)-$, and r is 1, then i) either R^1 and R^2, or R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**; and/or ii) Ring A is not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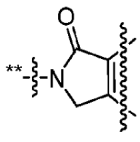
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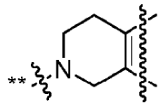
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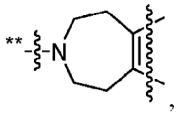
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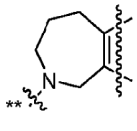
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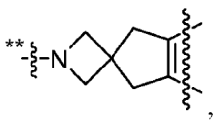
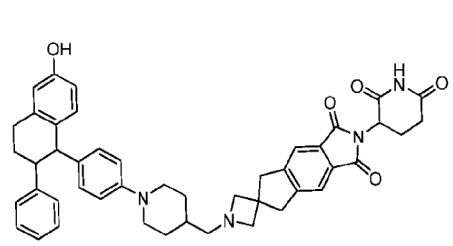

,

wherein ** denotes attachment to **L**, and/or

2) the compound is not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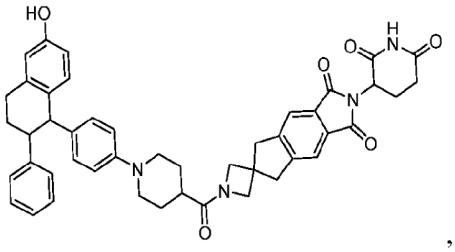
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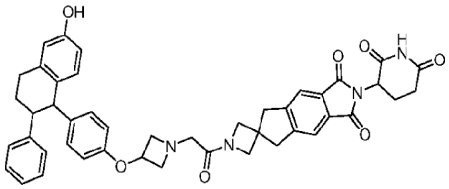
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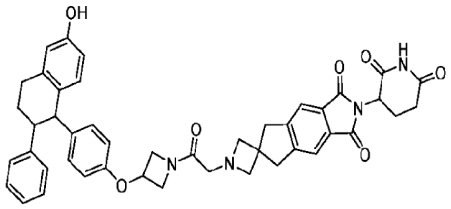
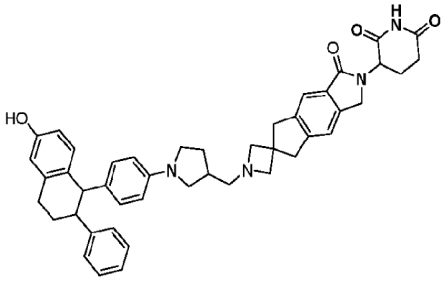
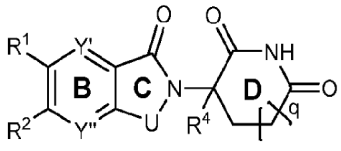
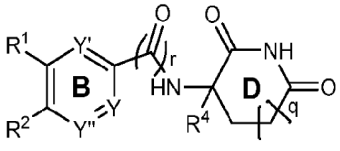

, and/or

,

or a pharmaceutically acceptable salt or stereoisomer thereof.

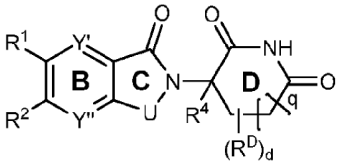
[0032] In certain embodiments, **C** is of Formula **I-1-i**


(**I-1-i**).

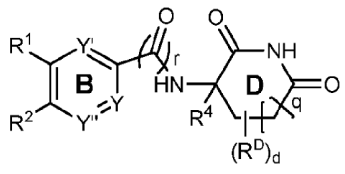
[0033] In certain embodiments, **C** is of Formula **I-1-ii**


(**I-1-ii**).

[0034] In certain embodiments, **C** is of Formula **I'-1-i**


(**I'-1-i**).

[0035] In certain embodiments, **C** is of Formula **I'-1-ii**



(I'-1-ii).

[0036] In certain embodiments, U is -CH_2- or -C(=O)-. In certain embodiments, U is -CH_2- or -C(=O)- when the bond between Y and U is present. In certain embodiments, U is -(C=O)-N(R^U)-* or -N=C(R^U)-* when the bond between Y and U is present.

[0037] In certain embodiments, R^1 is hydrogen, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-

membered rings and 1-5 heteroatoms selected from N, O, and S), $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0038] In certain embodiments, R^1 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0039] In certain embodiments, R^1 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0040] In certain embodiments, R^1 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0041] In certain embodiments, R^1 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0042] In certain embodiments, R^1 is hydrogen, halogen, or C_{1-6} alkoxy.

[0043] In certain embodiments, R^2 is ***-Cy^2-**, wherein * denotes attachment to **L**.

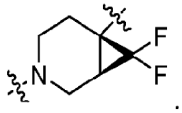
[0044] In certain embodiments, $-Cy^2-$ is C_{3-12} carbocyclylene (*e.g.*, cyclopropylene (C_3), cyclopropenylene (C_3), cyclobutylene (C_4), cyclobutenylene (C_4), cyclopentylene (C_5), cyclopentenylene (C_5), cyclohexylene (C_6), cyclohexenylene (C_6), cyclohexadienylene (C_6), cycloheptyl (C_7), cycloheptenylene (C_7), cycloheptadienylene (C_7), cycloheptatrienylene (C_7), cyclooctylene (C_8), cyclooctenylene (C_8), bicyclo[2.2.1]heptanylene (C_7), bicyclo[2.2.2]octanylene (C_8), cyclononylene (C_9), cyclononenylene (C_9), cyclodecylene (C_{10}),

cyclodecenylene (C_{10}), octahydro-1*H*-indenylene (C_9), decahydronaphthalenylene (C_{10}), or spiro[4.5]decanylene (C_{10})) or 3- to 12-membered heterocyclylene (*e.g.*, heterocyclylene comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the carbocyclylene or heterocyclylene is optionally substituted with one or more R^u.

[0045] In certain embodiments, *-Cy^2- is C_{5-12} fused carbocyclene or 5- to 12-membered fused heterocyclylene, wherein the carbocyclene or heterocyclylene is optionally substituted with one or more R^u.

[0046] In certain embodiments, *-Cy^2- is 5- to 12-membered fused heterocyclylene comprising 1 or 2 nitrogen atoms, wherein the heterocyclene is optionally substituted with one or more R^u.

[0047] In certain embodiments, *-Cy^2- is



.

[0048] In certain embodiments, R^1 and R^2, together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})) or 5- to 16-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 5- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S).

[0049] In certain embodiments, Y" is N or CR^3.

[0050] In certain embodiments, R^3 is hydrogen, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino,

ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0051] In certain embodiments, R^3 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0052] In certain embodiments, R^3 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino,

alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0053] In certain embodiments, R^3 is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0054] In certain embodiments, R^3 is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0055] In certain embodiments, R^3 is hydrogen, halogen, or C_{1-6} alkoxy.

[0056] In certain embodiments, R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})) or 5- to 16-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S).

[0057] In certain embodiments, R^1 and R^2, and R^2 and R^3, do not both form Ring A attached to **L.**

[0058] In certain embodiments, Y' is N or $CR^{Y'}$.

[0059] In certain embodiments, $R^{Y'}$ is hydrogen, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino,

ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0060] In certain embodiments, $R^{Y'}$ is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0061] In certain embodiments, $R^{Y'}$ is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0062] In certain embodiments, $R^{Y'}$ is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0063] In certain embodiments, $R^{Y'}$ is hydrogen, halogen, or C_{1-6} alkoxy.

[0064] In certain embodiments, i) when the bond between Y and U is absent, then r is 0 or 1, Y is N or CR^Y, and U is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u.

[0065] In certain embodiments, Y is N. In certain embodiments, Y is CR^Y.

[0066] In certain embodiments, R^Y is hydrogen, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0067] In certain embodiments, R^Y is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0068] In certain embodiments, R^Y is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0069] In certain embodiments, R^Y is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0070] In certain embodiments, R^Y is hydrogen, halogen, or C_{1-6} alkoxy.

[0071] In certain embodiments, ii) when the bond between Y and U is present, then r is 1, Y is C, and U is -CH_2-, -C(=O)-, -(C=O)-N(R^U)-*, or -N=C(R^U)-*.

[0072] In certain embodiments, R^U is H or C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)) optionally substituted with one or more R^u, and * denotes attachment to Ring B.

[0073] In certain embodiments, R^4 is hydrogen, deuterium, C_{1-6} haloalkyl (e.g., C_{1-6} alkyl comprising 1-6 halogen atoms selected from F, Cl, Br, and I), or C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)).

[0074] In certain embodiments, each R^D is independently oxo, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino,

ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0075] In certain embodiments, each R^D is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0076] In certain embodiments, each R^D is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0077] In certain embodiments, each R^D is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl,

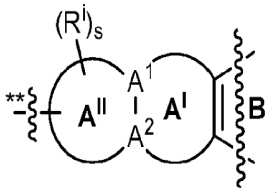
wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0078] In certain embodiments, d is an integer from 0 to 4. In certain embodiments, d is 0. In certain embodiments, d is 1. In certain embodiments, d is 2. In certain embodiments, d is 3. In certain embodiments, d is 4.

[0079] In certain embodiments, q is an integer from 0 to 2. In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2.

[0080] In certain embodiments, Ring A is optionally substituted 7- to 16-membered fused heterocycle.

[0081] In certain embodiments, Ring A is



,

wherein:

** denotes attachment to **L**;

Ring A^I and Ring A^{II} are independently C_{4-8} carbocycle or 4- to 8-membered heterocycle; wherein at least one of Ring A^{III} and Ring A^{IV} is 4- to 8-membered heterocycle;

A^1 and A^2 are independently C, CR^{Ax}, or N;

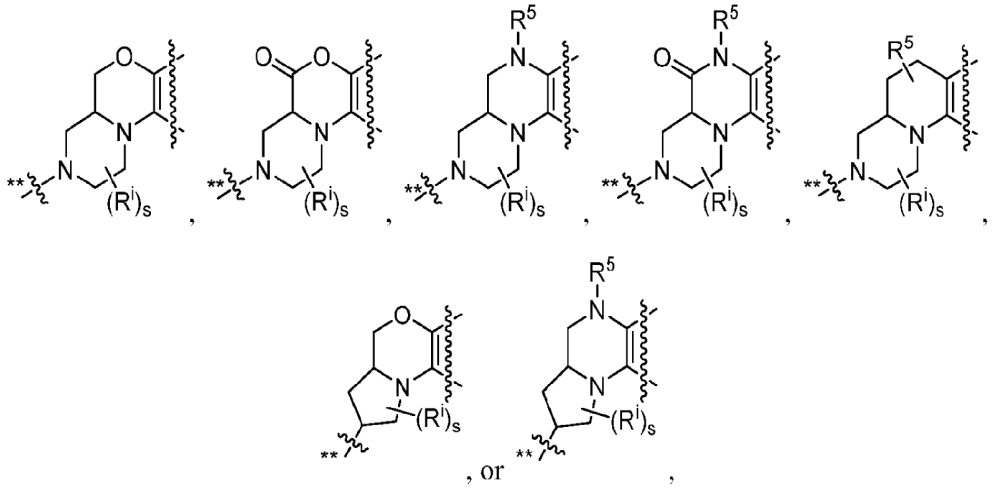
R^{Ax} is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits,

wherein each R^i may independently be present on either Ring A^I or Ring A^{II}.

[0082] In certain embodiments, Ring A is



wherein:

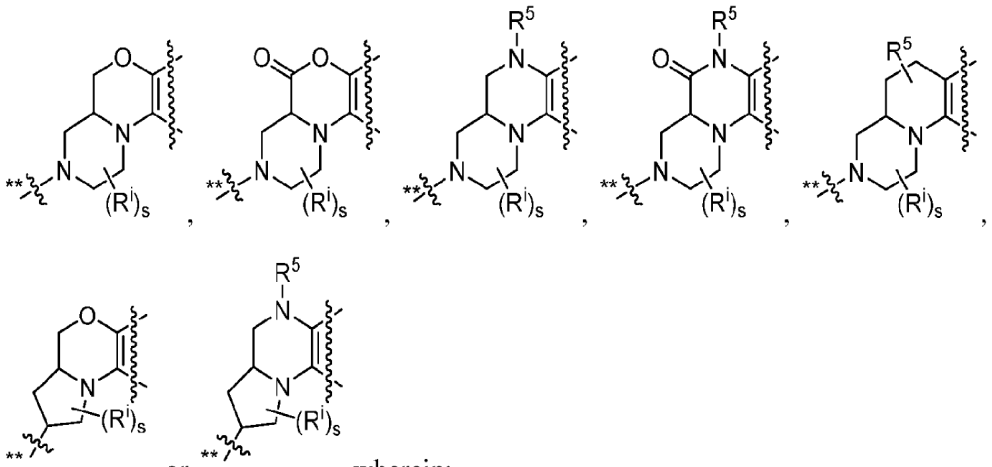
** denotes attachment to **L**;

R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits.

[0083] In certain embodiments, Ring A is



, or ,wherein:

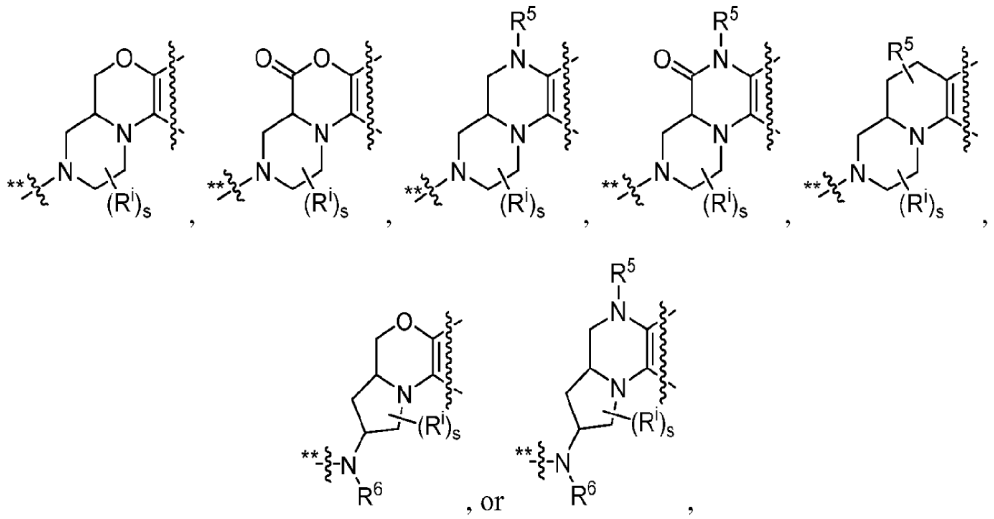
** denotes attachment to **L**;

R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits.

[0084] In certain embodiments, Ring A is



, or ,

wherein:

** denotes attachment to **L**;

R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

each R^6 is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits.

[0085] In certain embodiments, Ring A^I and Ring A^{II} are independently C_{4-8} carbocycle (e.g., cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), or cyclooctenyl (C_8)) or 4- to 8-membered heterocycle (*e.g.*, heterocyclyl comprising one or two 4- to 8-membered rings and 1-4 heteroatoms selected from N, O, and S); wherein at least one of Ring A^{III} and Ring A^{IV} is 4- to 8-membered heterocycle.

[0086] In certain embodiments, A^1 and A^2 are independently C, CR^{Ax}, or N.

[0087] In certain embodiments, R^{Ax} is hydrogen, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-

butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0088] In certain embodiments, R^{Ax} is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0089] In certain embodiments, R^{Ax} is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0090] In certain embodiments, R^{Ax} is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0091] In certain embodiments, R^6 is hydrogen, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0092] In certain embodiments, R^6 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, 5- to 6-membered heteroaryl, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0093] In certain embodiments, R^6 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

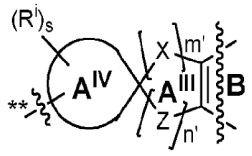
[0094] In certain embodiments, R^6 is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0095] In certain embodiments, Ring A is optionally substituted with one or more R^u.

[0096] In certain embodiments, R^u is R^{Ax}. In certain embodiments, R^u is R^5. In certain embodiments, R^u is R^i.

[0097] In certain embodiments, Ring A is optionally substituted 7- to 16-membered spiro heterocycle.

[0098] In certain embodiments, Ring A is:



,

wherein:

** denotes attachment to **L**;

Ring A^2 is C_{3-8} carbocycle or 3- to 8-membered heterocycle;

each X is independently $-C(R^{X1})_2-$, $-NR^{X2}-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$;

each Z is independently $-C(R^{Z1})_2-$, $-NR^{Z2}-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$;

each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

two geminal R^{X1} or two geminal R^{Z1} together form oxo; or

two R^{X1} or two R^{Z1}, together with the intervening carbon atom(s), form C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u;

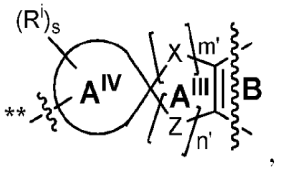
each occurrence of R^{X2} and R^{Z2} is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

m' and n' are independently an integer selected from 0-3, wherein m' and n' are not both 0;

each R^i is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^cS(=O)R^a$, -$NR^cS(=O)_2OR^b$, -$NR^cS(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$OS(=O)_2R^a$, -$OS(=O)_2OR^b$, -$OS(=O)_2NR^cR^d$, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits.

[0099] In certain embodiments, Ring A is



,

wherein:

** denotes attachment to **L**;

Ring A^{IV} is C_{3-8} carbocycle or 3- to 8-membered heterocycle;

each X is independently -$C(R^{X1})_2$-, -NR^{X2}-, -O-, -S-, -S(=O)-, or -$S(=O)_2$-;

each Z is independently -$C(R^{Z1})_2$-, -NR^{Z2}-, -O-, -S-, -S(=O)-, or -$S(=O)_2$-;

each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^cS(=O)R^a$, -$NR^cS(=O)_2OR^b$, -$NR^cS(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$OS(=O)_2R^a$, -$OS(=O)_2OR^b$, -$OS(=O)_2NR^cR^d$, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

two geminal R^{X1} or two geminal R^{Z1} together form oxo; or

two R^{X1} or two R^{Z1}, together with the intervening carbon atom(s), form C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u;

each occurrence of R^{X2} and R^{Z2} is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

m' and n' are independently an integer selected from 0-3, wherein m' and n' are not both 0;

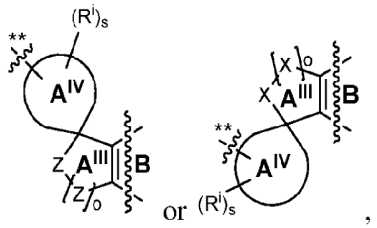
s is an integer selected from 0 to 8, as valency permits, and

each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u,

provided that when none of m' and n' is 0, then Ring A^1 is 4- to 9-membered heterocycle.

[0100] In certain embodiments, Ring A is:

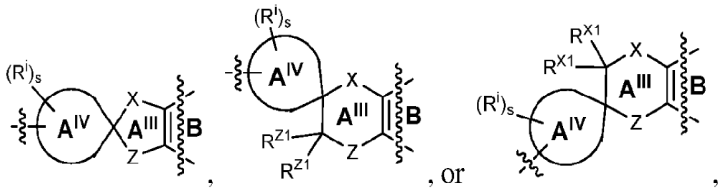
1)



,

wherein o is 0 or 1; or

2)



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wherein ** denotes attachment to **L**.

[0101] In certain embodiments, Ring A^{IV} is C_{3-8} carbocycle (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), or bicyclo[2.2.2]octanyl (C_8)) or 3- to 8-membered heterocycle (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S).

[0102] In certain embodiments, each X is independently -$C(R^{X1})_2$-, -NR^{X2}-, -O-, -S-, -S(=O)-, or -$S(=O)_2$-. In certain embodiments, each X is independently -$C(R^{X1})_2$-, -NR^{X2}-, and -O-.

[0103] In certain embodiments, each Z is independently -$C(R^{Z1})_2$-, -NR^{Z2}-, -O-, -S-, -S(=O)-, or -$S(=O)_2$-. In certain embodiments, each Z is independently -$C(R^{Z1})_2$-, -NR^{Z2}-, or -O-.

[0104] In certain embodiments, each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$,

$-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0105] In certain embodiments, each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0106] In certain embodiments, each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0107] In certain embodiments, each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0108] In certain embodiments, each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0109] In certain embodiments, two geminal R^{X1} or two geminal R^{Z1} together form oxo.

[0110] In certain embodiments, two R^{X1} or two R^{Z1}, together with the intervening carbon atom(s), form C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

[0111] In certain embodiments, two geminal R^{X1} or two geminal R^{Z1}, together with the carbon atom to which they are attached, form C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

[0112] In certain embodiments, each occurrence of R^{X2} and R^{Z2} is independently hydrogen or C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)) optionally substituted with one or more R^u.

[0113] In certain embodiments, m' is an integer selected from 0 to 3. In certain embodiments, m' is 0. In certain embodiments, m' is 1. In certain embodiments, m' is 2. In certain embodiments, m' is 3.

[0114] In certain embodiments, n' is an integer selected from 0 to 3. In certain embodiments, n' is 0. In certain embodiments, n' is 1. In certain embodiments, n' is 2. In certain embodiments, n' is 3.

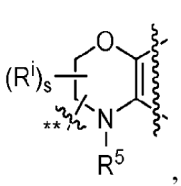
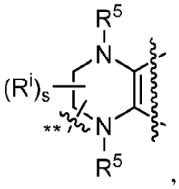
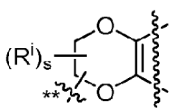
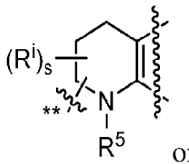
[0115] In certain embodiments, m' and n' are not both 0.

[0116] In certain embodiments, Ring A is optionally substituted with one or more R^u.

[0117] In certain embodiments, R^u is R^{X1}. In certain embodiments, R^u is R^{X2}. In certain embodiments, R^u is R^{Z1}. In certain embodiments, R^u is R^{Z2}. In certain embodiments, R^u is R^i.

[0118] In certain embodiments, Ring A is optionally substituted 5- to 6-membered heterocycle.

[0119] In certain embodiments, Ring A is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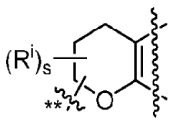

,wherein:

** denotes attachment to **L**;

R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits.

[0120] In certain embodiments, Ring A is optionally substituted with one or more R^u.

[0121] In certain embodiments, R^u is R^5. In certain embodiments, R^u is R^i.

[0122] In certain embodiments, R^5 is hydrogen or C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)) optionally substituted with one or more R^u.

[0123] In certain embodiments, each R^i is independently oxo, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, -

$NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0124] In certain embodiments, each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0125] In certain embodiments, each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0126] In certain embodiments, each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0127] In certain embodiments, each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0128] In certain embodiments, s is 0. In certain embodiments, s is 1. In certain embodiments, s is 2. In certain embodiments, s is 3. In certain embodiments, s is 4. In certain embodiments, s is 5. In certain embodiments, s is 6. In certain embodiments, s is 7. In certain embodiments, s is 8.

[0129] In certain embodiments, each of X^{T1}, X^{T2}, X^{T3}, and X^{T4} is CR^T.

[0130] In certain embodiments, each of X^{T1}, X^{T2}, X^{T3}, and X^{T4} is CH. In certain embodiments, each of X^{T1} and X^{T4} is CH, one of X^{T2} and X^{T3} is CH, and the other one of X^{T2} and X^{T3} is CF. In certain embodiments, one of X^{T1} and X^{T4} is CF or $C(OCH_3)$, the other one of X^{T1} and X^{T4} is CH, and each X^{T2} and X^{T3} is CH. In certain embodiments, X^{T1} is $C(OCH_3)$, X^{T3} is CF, and each of X^{T2}

and X^{T4} is CH. In certain embodiments, X^{T2} is CF, X^{T4} is $C(OCH_3)$, and each of X^{T1} and X^{T3} is CH. In certain embodiments, X^{T1} is $C(OCH_3)$, X^{T2} is CF, and each of X^{T3} and X^{T4} is CH.

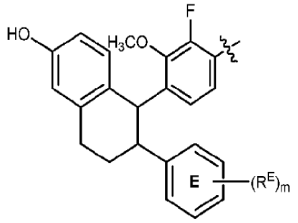
[0131] In certain embodiments, one of X^{T1}, X^{T2}, X^{T3}, and X^{T4} is N.

[0132] In certain embodiments, one of X^{T1} and X^{T4} is N, the other one of X^{T1} and X^{T4} is CH, and each of X^{T2} and X^{T3} is CH. In certain embodiments, one of X^{T2} and X^{T3} is N, the other one of X^{T2} and X^{T3} is CH, and each of X^{T1} and X^{T4} is CH.

[0133] In certain embodiments, two of X^{T1}, X^{T2}, X^{T3}, and X^{T4} are N.

[0134] In certain embodiments, each of X^{T1} and X^{T4} is CH, and each of X^{T2} and X^{T3} is N.

[0135] In certain embodiments, T is



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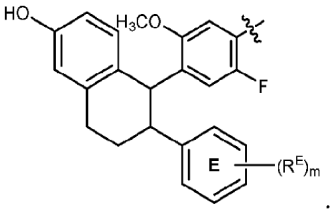

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[0136] In certain embodiments, each R^T is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

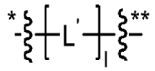
[0137] In certain embodiments, each R^T is independently hydrogen, C_{1-6} alkoxy, or halogen.

[0138] In certain embodiments, each R^E is independently halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0139] In certain embodiments, R^E is halogen.

[0140] In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 4. In certain embodiments, m is 5.

[0141] In certain embodiments, **L** is of Formula **I'-3**:



(I'-3),

wherein:

* denotes attachment to **T**, and ** denotes attachment to **C**;

each L' is independently C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{3-12} carbocyclylene, 3- to 12-membered heterocyclylene, C_{6-10} arylene, 5- to 10-membered heteroarylene, -C(=O)-, -C(=O)N(R^L)-, -C(=O)O-, -N(R^L)-, -O-, -S-, or -S(=O)$_2$-, wherein the alkylene, heteroalkylene, alkenylene, alkynylene, carbocyclylene, heterocyclylene, arylene, or heteroarylene is optionally substituted with one or more R^u;

each occurrence of R^L is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, -S(=O)$_2R^a$, -S(=O)$_2OR^b$, -S(=O)$_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

l is an integer selected from 0 to 10,

[0142] In certain embodiments, each L' is independently C_{1-6} alkylene (*e.g.*, methylene (-CH_2-), ethylene (-CH_2CH_2-), *n*-propylene (-$CH_2CH_2CH_2$-), *n*-butylene (-$CH_2CH_2CH_2CH_2$-), *n*-pentylene (-$CH_2CH_2CH_2CH_2CH_2$-), and *n*-hexylene (-$CH_2CH_2CH_2CH_2CH_2CH_2$-)), C_{1-6} heteroalkylene (*e.g.*, C_{1-6} heteroalkylene comprising 1-5 heteroatoms selected from N, O, and S), C_{2-6} alkenylene (*e.g.*, ethenylene (C_2), 1-propenylene (C_3), 2-propenylene (C_3), 1-butenylene (C_4), 2-butenylene (C_4), butadienylene (C_4), pentenylene (C_5), pentadienylene (C_5), or hexenylene (C_6)), C_{2-6} alkynylene (*e.g.*, ethynylene (C_2), 1-propynylene (C_3), 2-propynylene (C_3), 1-butynylene (C_4), 2-butynylene (C_4), pentynylene (C_5), or hexynylene (C_6)), C_{3-12} carbocyclylene (*e.g.*, cyclopropylene (C_3), cyclopropenylene (C_3), cyclobutylene (C_4), cyclobutenylene (C_4), cyclopentylene (C_5), cyclopentenylene (C_5), cyclohexylene (C_6), cyclohexenylene (C_6), cyclohexadienylene (C_6), cycloheptylene (C_7), cycloheptenylene (C_7), cycloheptadienylene (C_7), cycloheptatrienylene (C_7), cyclooctylene (C_8), cyclooctenylene (C_8), bicyclo[2.2.1]heptanylene (C_7), bicyclo[2.2.2]octanylene (C_8), cyclononylene (C_9), cyclononenylene (C_9), cyclodecylene (C_{10}), cyclodecenylene (C_{10}), octahydro-1*H*-indenylene (C_9), decahydronaphthalenylene (C_{10}), or spiro[4.5]decanylene (C_{10})), 3- to 12-membered heterocyclylene (*e.g.*, heterocyclylene comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} arylene (*e.g.*, phenylene or naphthylene), 5- to 10-membered heteroarylene (*e.g.*, heteroarylene comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -C(=O)-, -

$C(=O)N(R^L)$-, -$C(=O)O$-, -$N(R^L)$-, -O-, -S-, or -$S(=O)_2$-, wherein the alkylene, alkenylene, carbocyclylene, heterocyclylene, arylene, or heteroarylene is optionally substituted with one or more R^u.

[0143] In certain embodiments, each L' is independently C_{1-6} alkylene, C_{3-12} carbocyclylene, 3- to 12-membered heterocyclylene, -C(=O)-, $-C(=O)N(R^L)$-, -$C(=O)O$-, -$N(R^L)$-, or -O-, wherein the alkylene, carbocyclylene, or heterocyclylene is optionally substituted with one or more R^u.

[0144] In certain embodiments, each occurrence of R^L is independently hydrogen, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0145] In certain embodiments, each occurrence of R^L is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, C_6 aryl, 5- to 6-membered heteroaryl, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

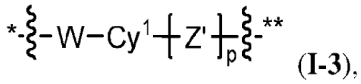
[0146] In certain embodiments, each occurrence of R^L is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, -$S(=O)_2R^a$, -$S(=O)_2OR^b$,

$-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0147] In certain embodiments, each occurrence of R^L is independently hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0148] In certain embodiments, l is 0. In certain embodiments, l is 1. In certain embodiments, l is 2. In certain embodiments, l is 3. In certain embodiments, l is 4. In certain embodiments, l is 5. In certain embodiments, l is 6. In certain embodiments, l is 7. In certain embodiments, l is 8. In certain embodiments, l is 9. In certain embodiments, l is 10.

[0149] In certain embodiments, **L** is of Formula **I-3**:



(I-3),

wherein:

* denotes attachment to **T** and ** denotes attachment to **C**;

W is absent; or

W is C_{1-3} alkylene, -O-, $-NR^W$-, or -(C=O)- , wherein the alkylene is optionally substituted by one or more R^u;

Cy^1 is absent; or

Cy^1 is 6-membered heteroarylene, C_6 arylene, C_{3-12} carbocyclylene, or 3- to 12-membered heterocyclylene, wherein the arylene, heteroarylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u;

Z' is absent; or

each Z' is independently C_{1-3} alkylene, -O-, $-NR^W$-, -(C=O)-, C_{3-12} carbocyclylene, or 3- to 12-membered heterocyclylene, wherein the alkylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u;

R^W is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u; and

p is an integer selected from 0 to 8.

[0150] In certain embodiments, W is absent.

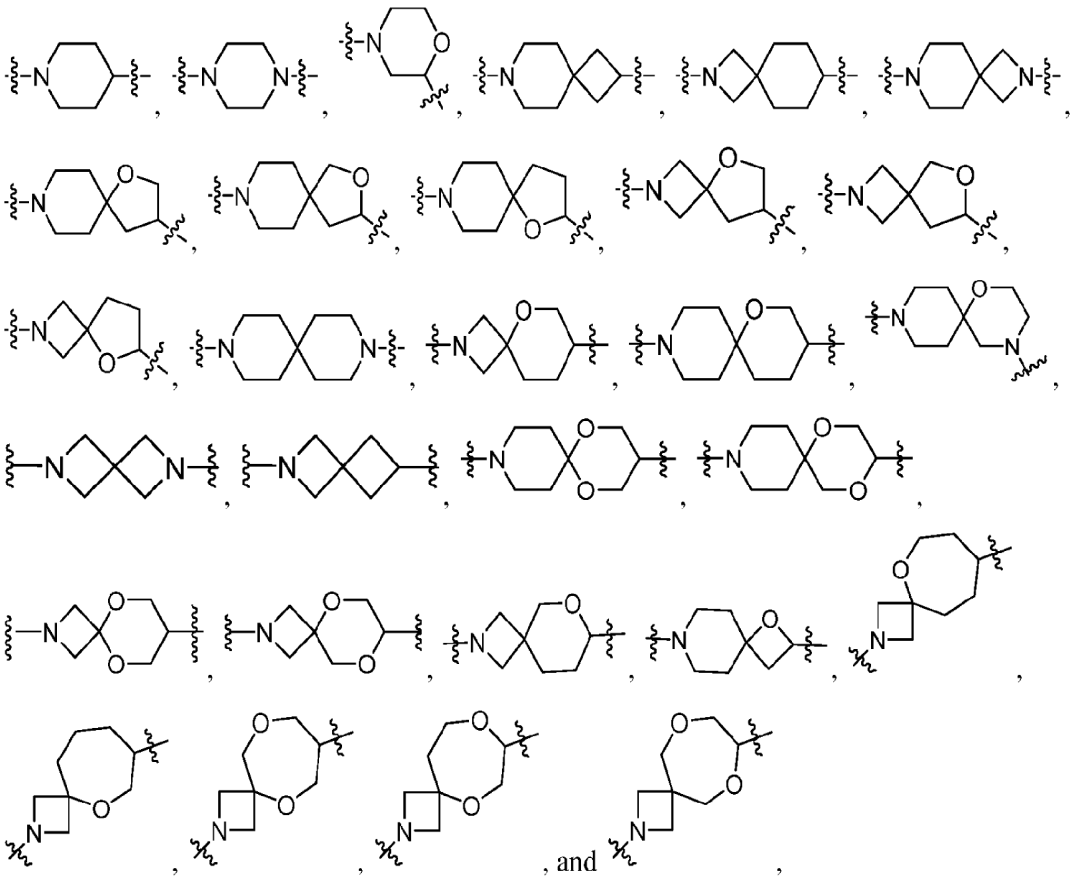
[0151] In certain embodiments, W is C_{1-3} alkylene (*e.g.*, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), or *n*-propylene ($-CH_2CH_2CH_2-$)), -O-, $-NR^W-$, or -(C=O)- , wherein the alkylene is optionally substituted by one or more R^u.

[0152] In certain embodiments, Cy^1 is absent.

[0153] In certain embodiments, Cy^1 is C_6 arylene (*i.e.*, phenylene), 6-membered heteroarylene (*e.g.*, heteroarylene comprising one 6-membered ring and 1-4 heteroatoms selected from N, O, and S), C_{3-12} carbocyclylene (*e.g.*, cyclopropylene (C_3), cyclopropenylene (C_3), cyclobutylene (C_4), cyclobutenylene (C_4), cyclopentylene (C_5), cyclopentenylene (C_5), cyclohexylene (C_6), cyclohexenylene (C_6), cyclohexadienylene (C_6), cycloheptylene (C_7), cycloheptenylene (C_7), cycloheptadienylene (C_7), cycloheptatrienylene (C_7), cyclooctylene (C_8), cyclooctenylene (C_8), bicyclo[2.2.1]heptanylene (C_7), bicyclo[2.2.2]octanylene (C_8), cyclononylene (C_9), cyclononenylene (C_9), cyclodecylene (C_{10}), cyclodecenylene (C_{10}), octahydro-1*H*-indenylene (C_9), decahydronaphthalenylene (C_{10}), or spiro[4.5]decanylene (C_{10})), or 3- to 12-membered heterocyclylene (*e.g.*, heterocyclylene comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the arylene, heteroarylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u.

[0154] In certain embodiments, Cy^1 is 3- to 12-membered heterocyclylene selected from morpholinylene, piperidinylene, piperazinylene, 7-azaspiro[3.5]nonanylene, 2,7-diazaspiro[3.5]nonanylene, 2-azaspiro[3.5]nonanylene, 2,7-diazaspiro[3.5]nonanylene, 1-oxa-8-azaspiro[4.5]decenylene, 2-oxa-8-azaspiro[4.5]decenylene, 5-oxa-2-azaspiro[3.4]octanylene, 6-oxa-2-azaspiro[3.4]octanylene, 3,9-diazaspiro[5.5]undecanylene, 5-oxa-2-azaspiro[3.5]nonanylene, 1-oxa-9-azaspiro[5.5]undecanylene, 1-oxa-4,9-diazaspiro[5.5]undecanylene, 2,6-diazaspiro[3.3]heptanylene, 2-azaspiro[3.3]heptanylene, 1,5-dioxa-9-azaspiro[5.5]undecanylene, 1,4-dioxa-9-azaspiro[5.5]undecanylene, 5,9-dioxa-2-azaspiro[3.5]nonanylene, 5,8-dioxa-2-azaspiro[3.5]nonanylene, 6-oxa-2-azaspiro[3.5]nonanylene, 1-oxa-7-azaspiro[3.5]nonanylene, 5-oxa-2-azaspiro[3.6]decenylene, 5-oxa-2-azaspiro[3.6]decenylene, 5,9-dioxa-2-azaspiro[3.6]decenylene, 5,8-dioxa-2-azaspiro[3.6]decenylene, and 6,9-dioxa-2-azaspiro[3.6]decenylene, wherein the heterocyclylene is optionally substituted by one or more R^u.

[0155] In certain embodiments, Cy^1 is 3- to 12-membered heterocyclylene selected from:



wherein the heterocyclylene is optionally substituted by one or more R^u.

[0156] In certain embodiments, Z' is absent.

[0157] In certain embodiments, each Z' is independently C_{1-3} alkylene (*e.g.*, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), or *n*-propylene ($-CH_2CH_2CH_2-$)), -O-, $-NR^W-$, -(C=O)-, C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), or 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u.

[0158] In certain embodiments, R^W is hydrogen or C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)) optionally substituted with one or more R^u.

[0159] In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 3. In certain embodiments, p is 4. In certain embodiments, p is 5. In certain embodiments, p is 6. In certain embodiments, p is 7. In certain embodiments, p is 8.

[0160] In certain embodiments, $-[Z']_p-$ is -C(=O)-, C_{1-6} alkylene, *-O-(C_{1-6} alkylene)-, *-(C_{1-6} alkylene)-(C(=O))-O-, *-(C_{1-6} alkylene)-O-, *-C(=O)-(C_{1-6} alkylene)-, *-(C_{1-6} alkylene)-C(=O)-, 3- to 12-membered heterocyclylene, *-C(=O)-(3- to 12-membered heterocyclylene)-, *-(3- to 12-membered heterocyclylene)-C(=O)-, *-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-, *-(C_{1-6} alkylene)-(3- to 12-membered heterocyclylene)-, *-(C_{1-6} alkylene)-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-, *-(C_{1-6} alkylene)-(3- to 12-membered heterocyclylene)-(C(=O))-, *-(C(=O))-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-, *-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-(C(=O))-, *-(C(=O))-(C_{1-6} alkylene)-(3- to 12-membered heterocyclylene)-, *-(C_{1-6} alkylene)-(C(=O))-(3- to 12-membered heterocyclylene)-, or *-(3- to 12-membered heterocyclylene)-(C(=O))-(C_{1-6} alkylene)-, wherein the alkylene or heterocyclylene is optionally substituted by one or more R^u, and *denotes attachment to **C**.

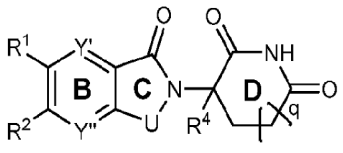
[0161] In certain embodiments, $-[Z']_p-$ is -C(=O)-, C_{1-6} alkylene, *-(C_{1-6} alkylene)-(C(=O))-O-, *-C(=O)-(C_{1-6} alkylene)-, *-(C_{1-6} alkylene)-C(=O)-, 3- to 12-membered heterocyclylene, *-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-, *-(C(=O))-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-, *-(C(=O))-(C_{1-6} alkylene)-(3- to 12-membered heterocyclylene)-, *-(C_{1-6} alkylene)-(C(=O))-(3- to 12-membered heterocyclylene)-, wherein the alkylene or heterocyclylene is optionally substituted by one or more R^u, and *denotes attachment to **C**.

[0162] In certain embodiments, L' is W. In certain embodiments, L' is Cy^1. In certain embodiments, L' is Z'.

[0163] In certain embodiments, l is p. In certain embodiments, l is p+1. In certain embodiments, l is p+2.

[0164] In certain embodiments,

C is of Formula **I-1-i**



(**I-1-i**),

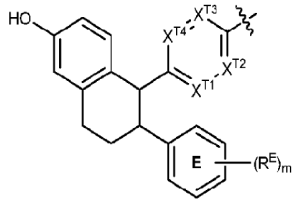
wherein:

R^1 and R^2, together with the intervening carbon atoms, form Ring A attached to **L**; or

R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**; and

Ring A is optionally substituted 7- to 16-membered fused heterocycle or optionally substituted 7- to 16-membered spiro heterocycle,

T is of Formula **I-2**:



(**I-2**),

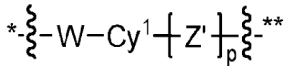
wherein:

each of X^{T1}, X^{T2}, X^{T3}, and X^{T4} is CR^T, wherein

i) X^{T1} is $C(OCH_3)$, X^{T3} is CF, and each of X^{T2} and X^{T4} is CH; or

ii) X^{T1} is $C(OCH_3)$, X^{T2} is CF, and each of X^{T3} and X^{T4} is CH, and

L is of Formula **I-3**:



(**I-3**),

wherein:

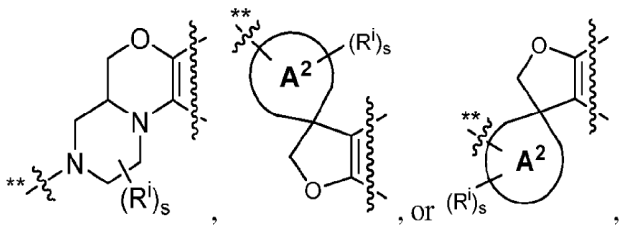
W is absent;

Cy^1 is C_{3-12} carbocyclylene or 3- to 12-membered heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted by one or more R^u;

each Z' is independently C_{1-3} alkylene optionally substituted by one or more R^u; and

p is an integer selected from 0 to 6.

[0165] In certain embodiments, Ring A is



wherein ** denotes attachment to **L**; s is an integer selected from 0 to 8, as valency permits; and Ring A^2 is C_{3-8} carbocycle or 3- to 8-membered heterocycle.

[0166] In certain embodiments, each R^a is independently C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0167] In certain embodiments, each R^a is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl.

[0168] In certain embodiments, each R^a is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl.

[0169] In certain embodiments, each R^a is independently C_{1-6} alkyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0170] In certain embodiments, each R^b is independently hydrogen, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7),

cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0171] In certain embodiments, each R^b is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl.

[0172] In certain embodiments, each R^b is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl.

[0173] In certain embodiments, each R^b is independently hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, or C_{2-6} alkynyl, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0174] In certain embodiments, each R^c and each R^d is independently hydrogen, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0175] In certain embodiments, each R^c and each R^d is independently hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, carbocyclyl, or heterocyclylis optionally substituted with one or more R^u.

[0176] In certain embodiments, R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the heterocyclyl is optionally substituted with one or more R^u.

[0177] In certain embodiments, R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z.

[0178] In certain embodiments, R^z is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl.

[0179] In certain embodiments, each R^u is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7),

cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl.

[0180] In certain embodiments, each R^u is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl.

[0181] In certain embodiments, each R^u is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl.

[0182] In certain embodiments, each R^u is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl or

heterocyclyl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl.

[0183] In certain embodiments, each R^u is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl or heterocyclyl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl.

[0184] In certain embodiments, two R^u, together with the carbon atom(s) to which they are attached, form C_{3-6} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), or cyclohexadienyl (C_6)) or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms selected from N, O, and S).

[0185] In certain embodiments, two geminal R^u, together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), or cyclohexadienyl (C_6)) or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms selected from N, O, and S).

[0186] Embodiments of the variables in any of the Formulae described herein, *e.g.*, Formulae **I** and **I'**, as applicable, are described below. Any of the variables can be any moiety as described in the embodiments below. In addition, the combination of any moieties described for any of the variables, as applicable, with any moieties described for any of the remaining variables, is also contemplated.

[0187] Without wishing to be limited by this statement, while various options for variables are described herein, it is understood that the present disclosure intends to encompass operable embodiments having combinations of the options. The disclosure may be interpreted as excluding the non-operable embodiments caused by certain combinations of the options. For example, while various options for variables X and Z are described herein, the disclosure may be interpreted as excluding structures for non-operable compounds caused by certain combinations of the options

(e.g., when two X or two Z are both nitrogen or both oxygen; or one of the two X or one of the two Z is nitrogen while the other is oxygen).

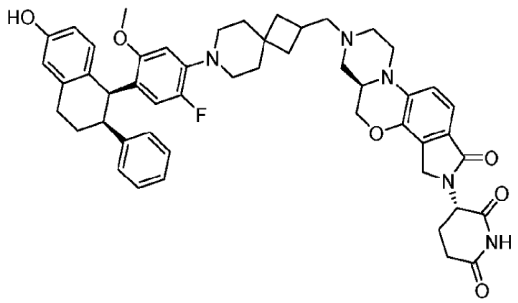
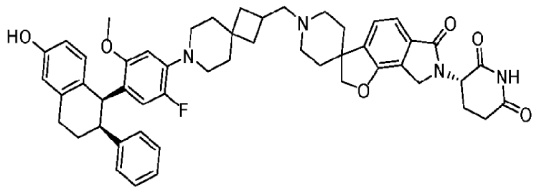
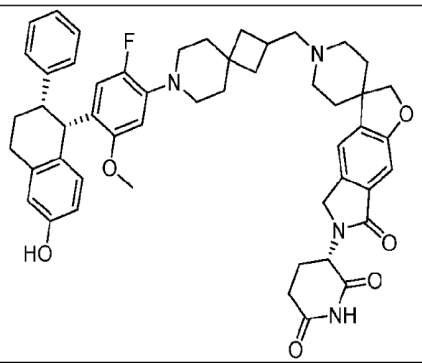
[0188] When a range of values is listed, each discrete value and sub-range within the range are also contemplated. For example, "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

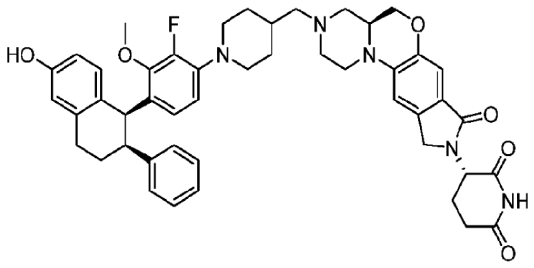
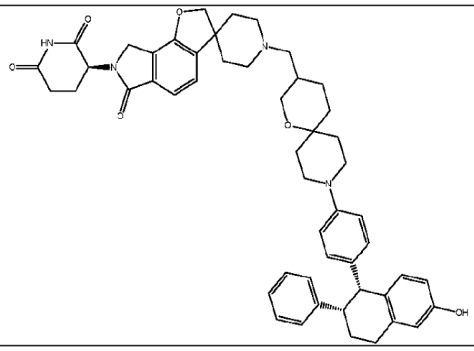
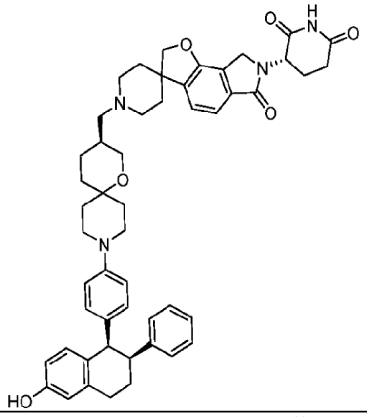
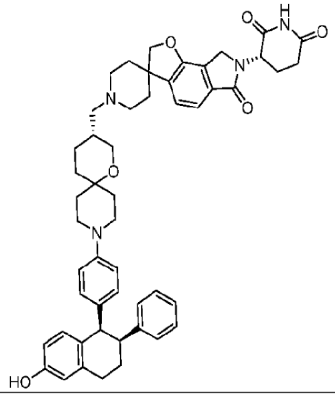
[0189]

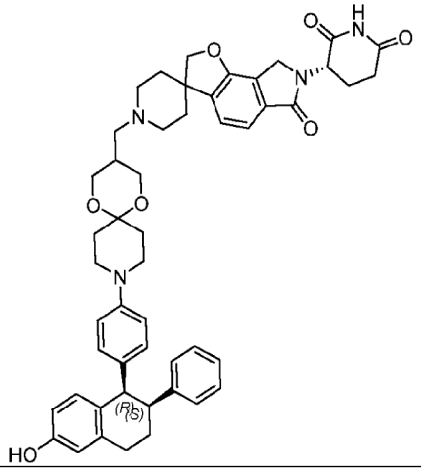
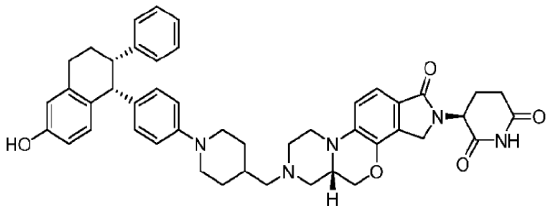
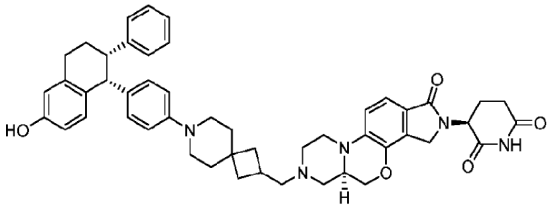
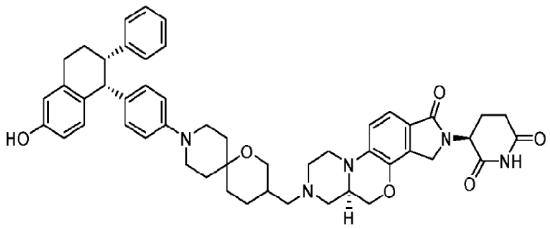
[0190] In certain embodiments, the compound is selected from the compounds in **Table X** below, or a pharmaceutically acceptable salt thereof.

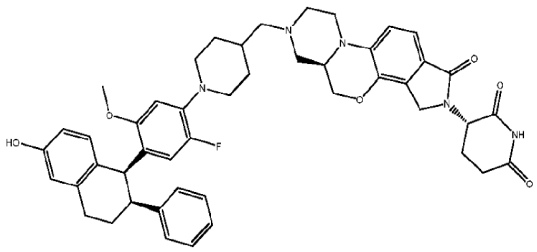
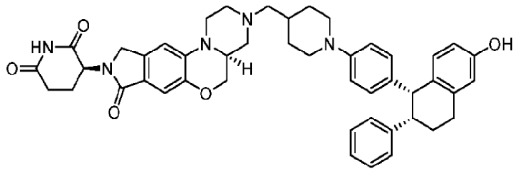
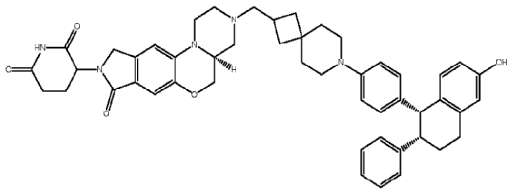
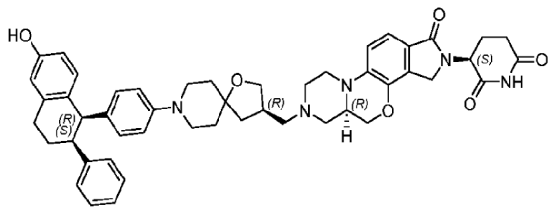
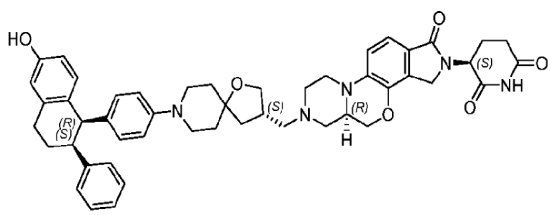
[0191] In certain embodiments, the compound is selected from the compounds in **Table X** below.

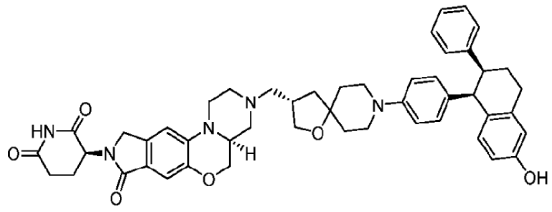
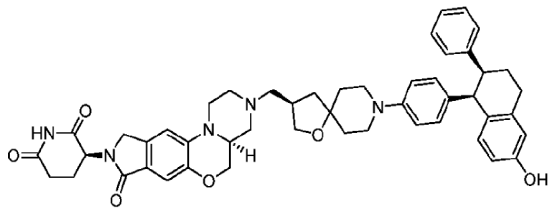
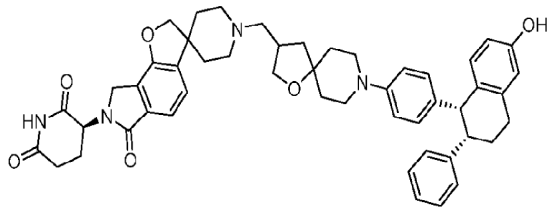
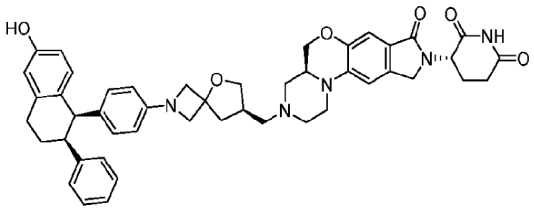
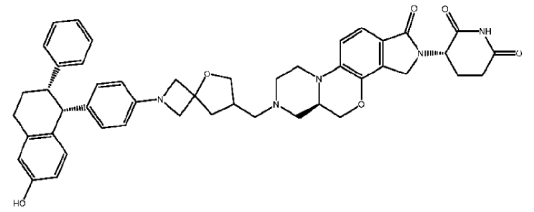
Table X

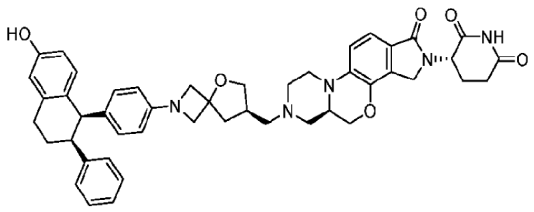
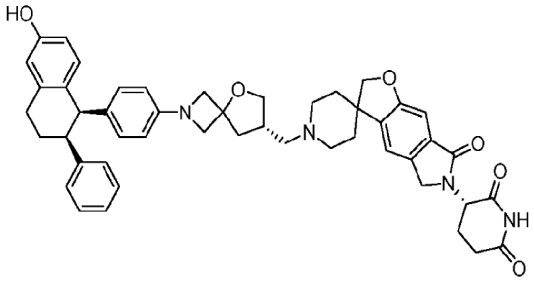
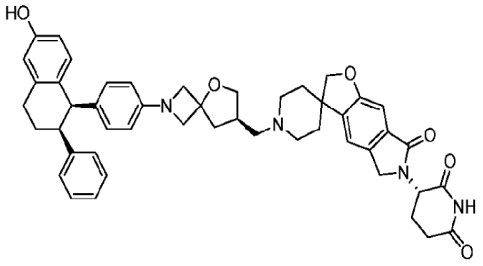
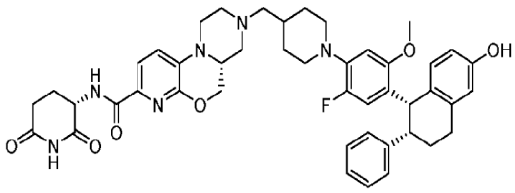
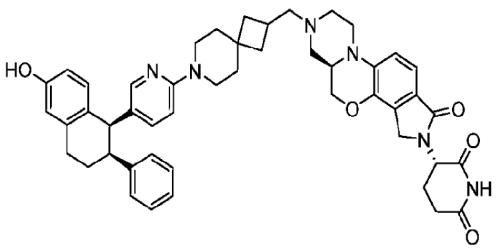
Compound No.	Structure	Chemical Name
A99		(S)-3-((R)-7-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A100		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A129		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

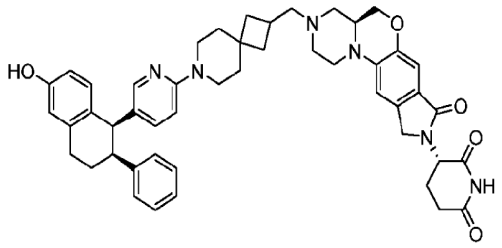
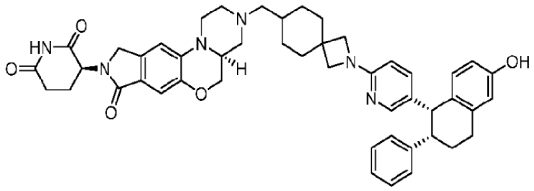
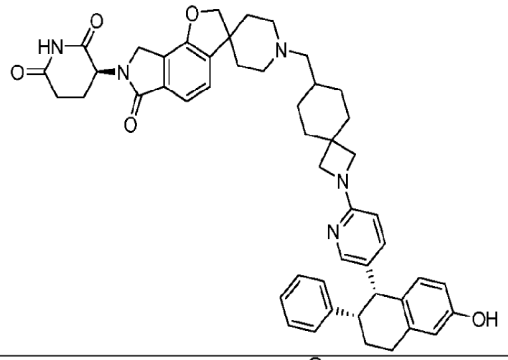
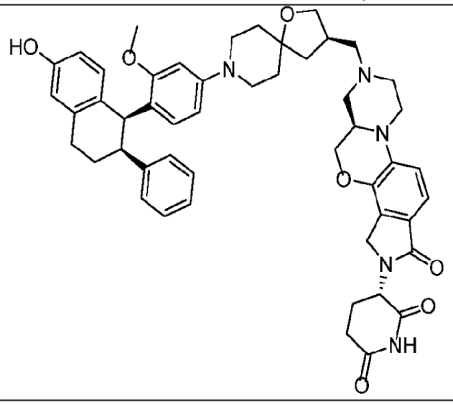
Compound No.	Structure	Chemical Name
A171		(S)-3-((S)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B366		(3S)-3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B366X		(S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B366Y		(S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

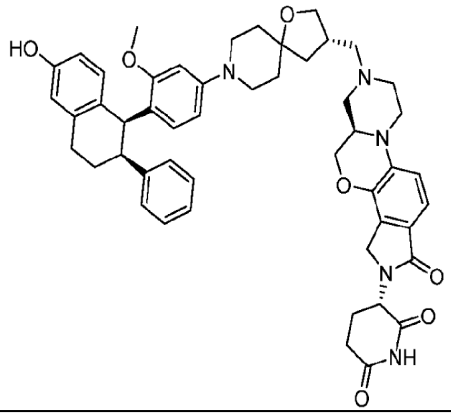
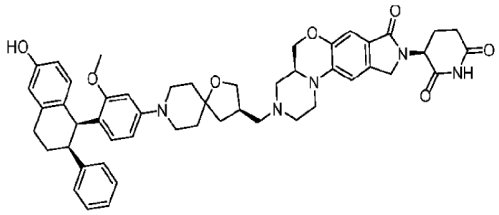
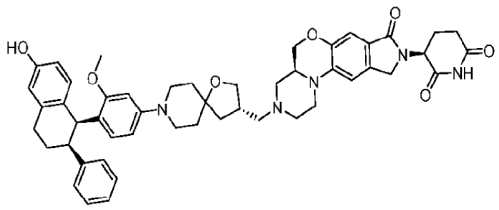
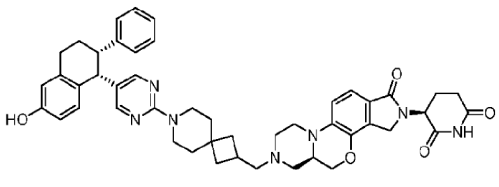
Compound No.	Structure	Chemical Name
B337X		(S)-3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B306X		(S)-3-((S)-7-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B308X		(S)-3-((R)-7-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B330X		(3S)-3-((5aR)-7-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

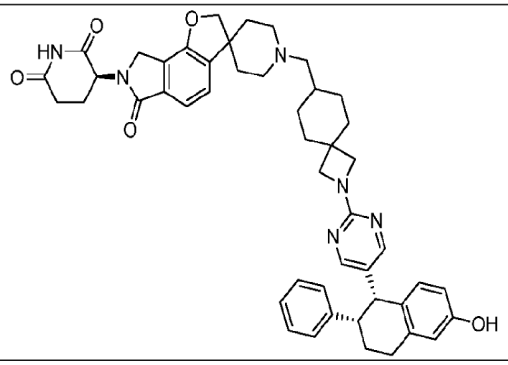
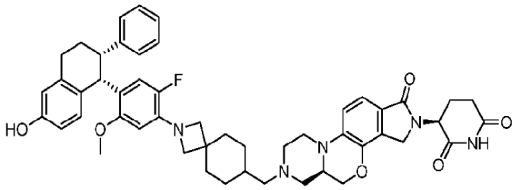
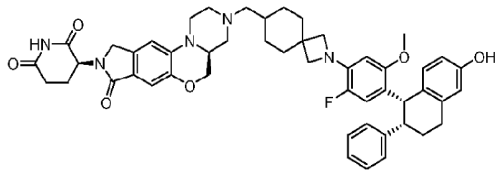
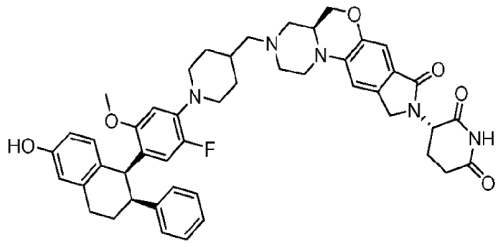
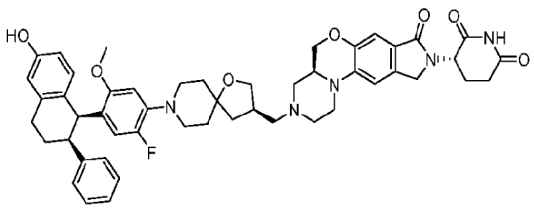
Compound No.	Structure	Chemical Name
A35		(S)-3-((R)-7-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B135X		(S)-3-((S)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B211		3-((S)-3-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B226X		(S)-3-((R)-7-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B226Y		(S)-3-((R)-7-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

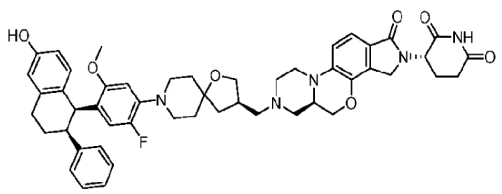
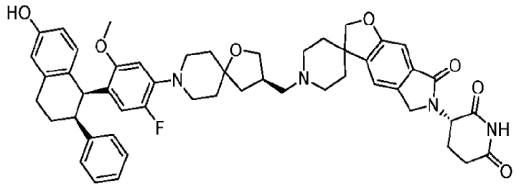
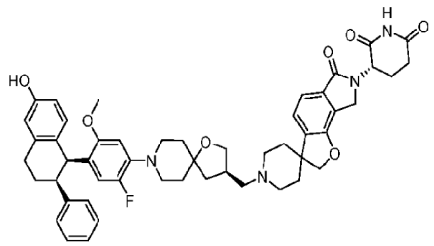
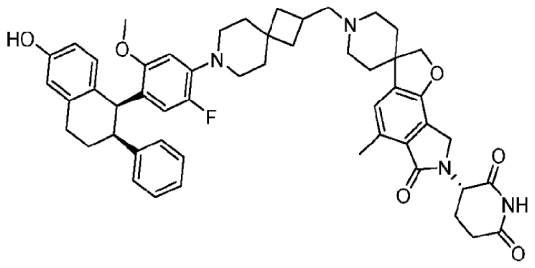
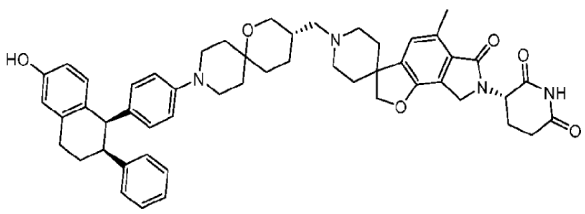
Compound No.	Structure	Chemical Name
B227X		(S)-3-((S)-3-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B227Y		(S)-3-((S)-3-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B229X		(3S)-3-(1'-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A73		(S)-3-((S)-3-(((R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A40		(3S)-3-((5aR)-7-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2

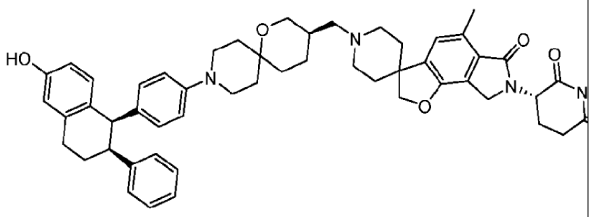
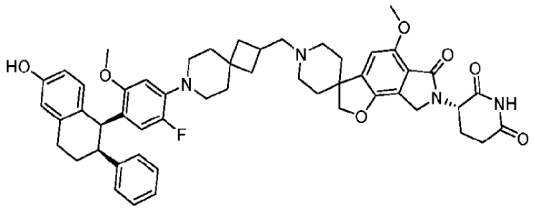
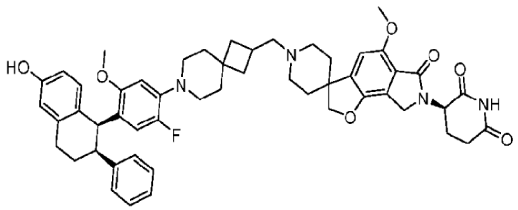
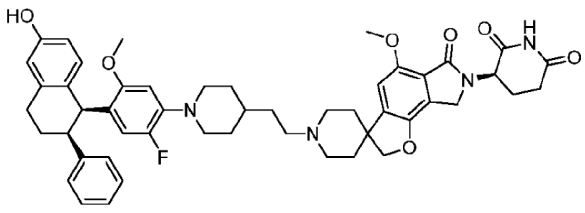
Compound No.	Structure	Chemical Name
		,3-e]isoindol-2-yl)piperidine-2,6-dione
A69		(S)-3-((R)-7-(((R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A76		(S)-3-(1'-(((S)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A77		(S)-3-(1'-(((R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A94		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A112		(S)-3-((R)-7-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2

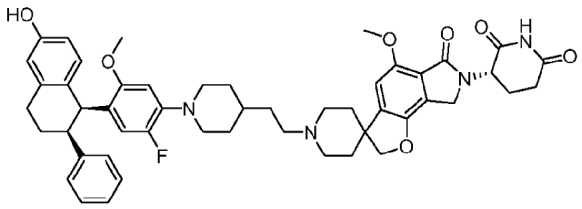
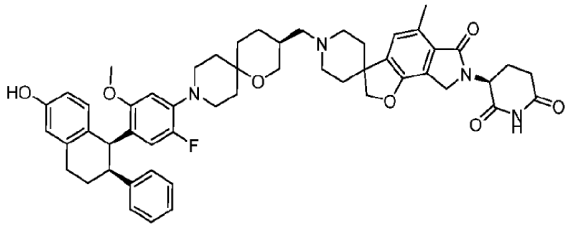
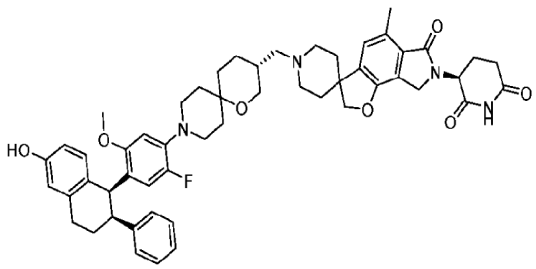
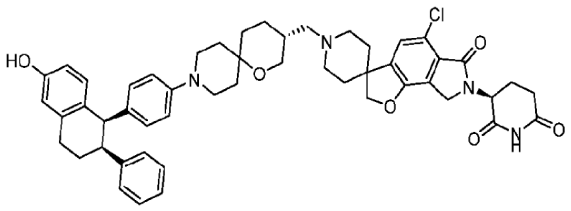
Compound No.	Structure	Chemical Name
		,3-e]isoindol-2-yl)piperidine-2,6-dione
A121		(S)-3-((S)-3-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A130		(S)-3-((S)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A131		(S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A133		(S)-3-((R)-7-(((R)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

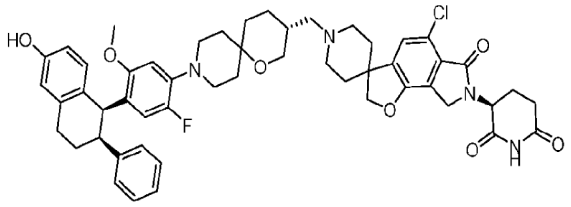
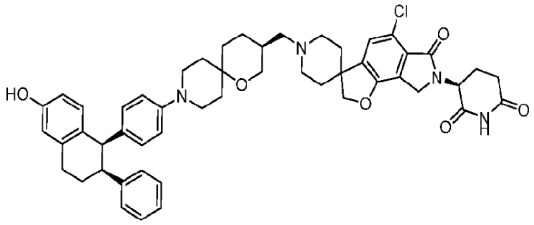
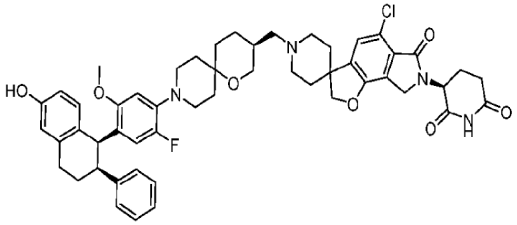
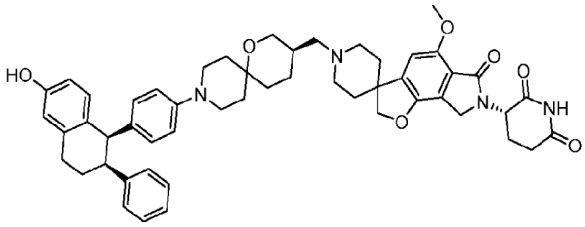
Compound No.	Structure	Chemical Name
A134		(S)-3-((R)-7-(((S)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A135		(S)-3-((S)-3-(((R)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A136		(S)-3-((S)-3-(((S)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A140		(S)-3-((R)-7-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

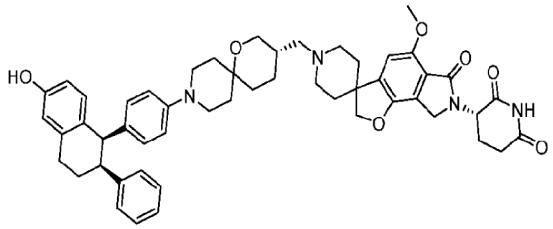
Compound No.	Structure	Chemical Name
A154		(S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A163		(S)-3-((R)-7-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A164		(S)-3-((S)-3-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A91		(S)-3-((S)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A173		(S)-3-((S)-3-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2

Compound No.	Structure	Chemical Name
		,3-f]isoindol-9-yl)piperidine-2,6-dione
A174		(S)-3-((R)-7-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-c]isoindol-2-yl)piperidine-2,6-dione
A175		(S)-3-(1'-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A176		(S)-3-(1'-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-c]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A203		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A209		(S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-

Compound No.	Structure	Chemical Name
		spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A210		(S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A222		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A223		(R)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A225		(R)-3-(1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Structure	Chemical Name
A226		(S)-3-(1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A227		(S)-3-(1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A230		(S)-3-(1'-(((R)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A231		(S)-3-(5-chloro-1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Structure	Chemical Name
A232		(S)-3-(5-chloro-1'-(((R)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A233		(S)-3-(5-chloro-1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A234		(S)-3-(5-chloro-1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A235		(S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Structure	Chemical Name
A236		(S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

[0192] In certain embodiments, the compound is selected from the compounds in Tables 1-3, or a pharmaceutically acceptable salt thereof.

[0193] In certain embodiments, the compound is selected from the compounds in Tables 1-3.

[0194] In certain embodiments, the compound is selected from the compounds in Tables 1 and 2, or a pharmaceutically acceptable salt thereof.

[0195] In certain embodiments, the compound is selected from the compounds in Tables 1 and 2.

[0196] In certain embodiments, the compound is selected from the compounds in Table 1, or a pharmaceutically acceptable salt thereof.

[0197] In certain embodiments, the compound is selected from the compounds in Table 1.

[0198] In certain embodiments, the compound is selected from the compounds in Table 2, or a pharmaceutically acceptable salt thereof.

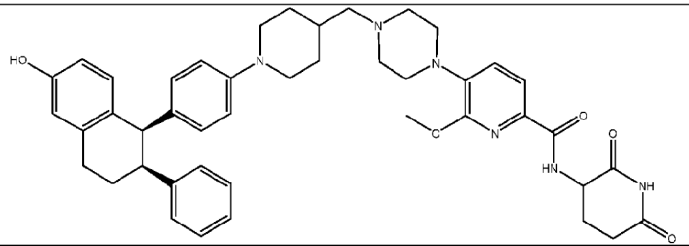
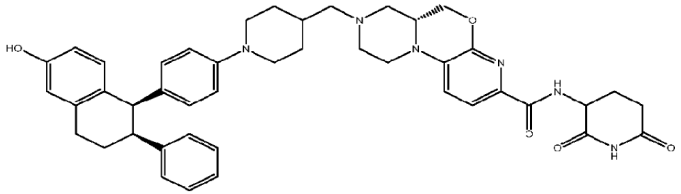
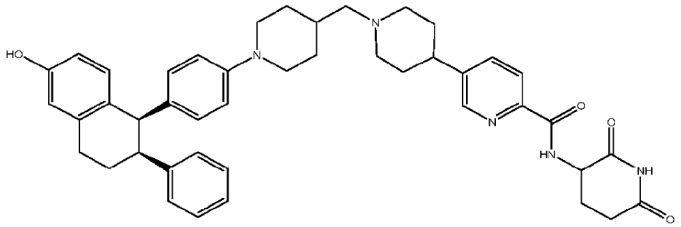
[0199] In certain embodiments, the compound is selected from the compounds in Table 2.

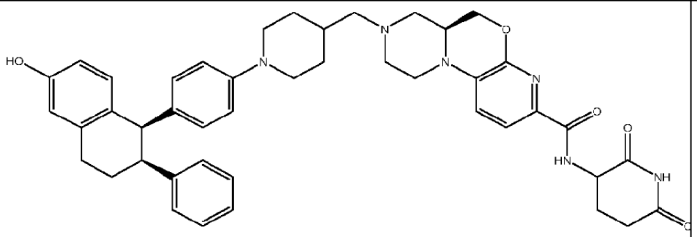
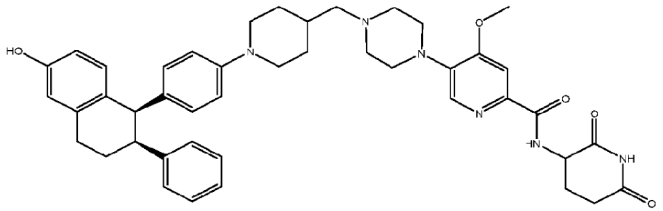
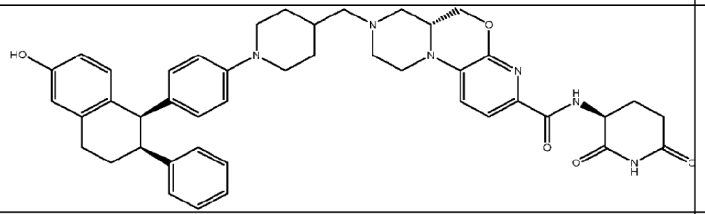
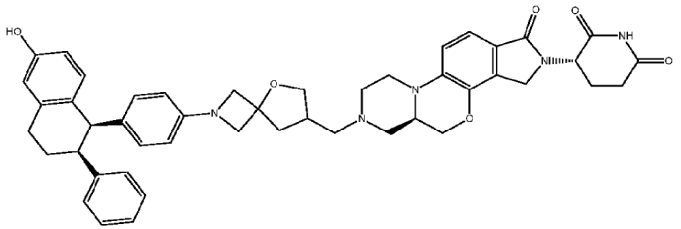
[0200] In certain embodiments, the compound is selected from the compounds in Table 3, or a pharmaceutically acceptable salt thereof.

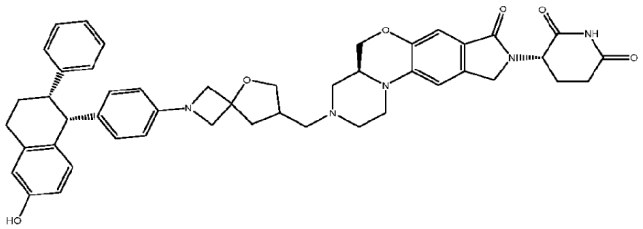
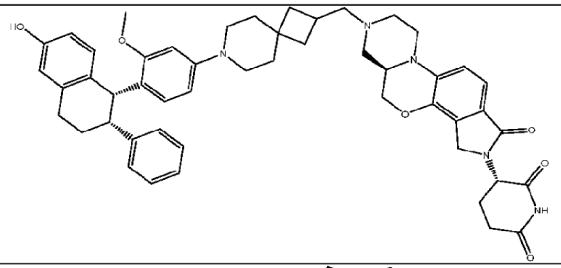
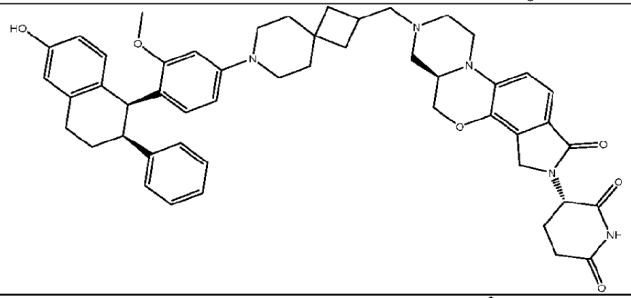
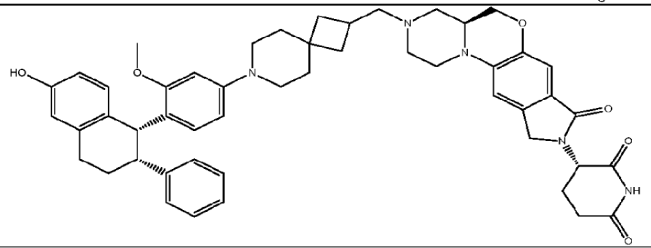
[0201] In certain embodiments, the compound is selected from the compounds in Table 3.

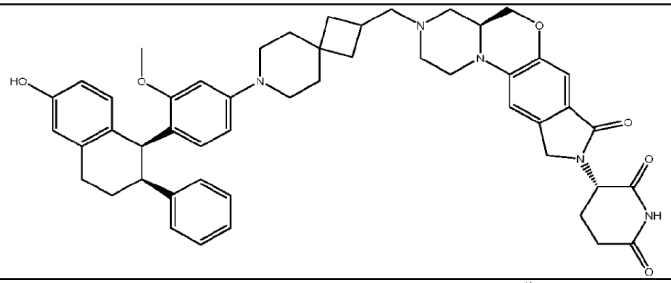
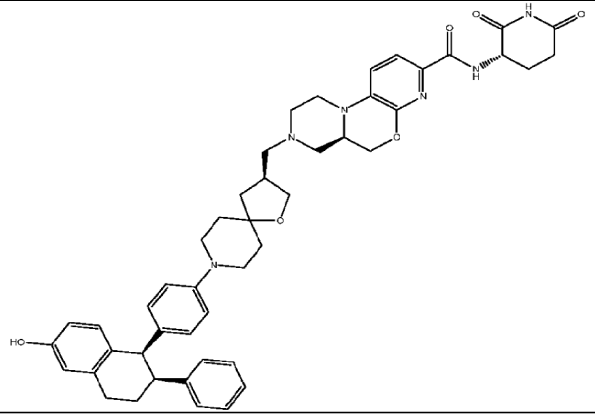
Table 1.

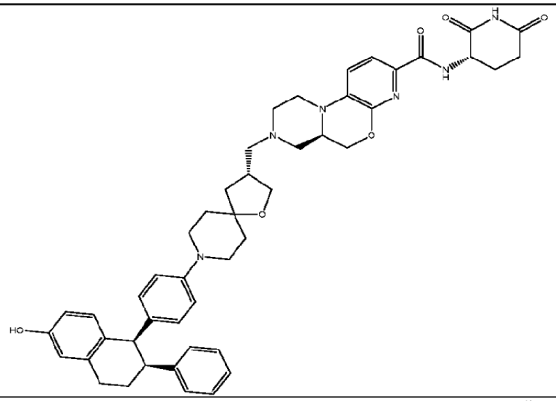
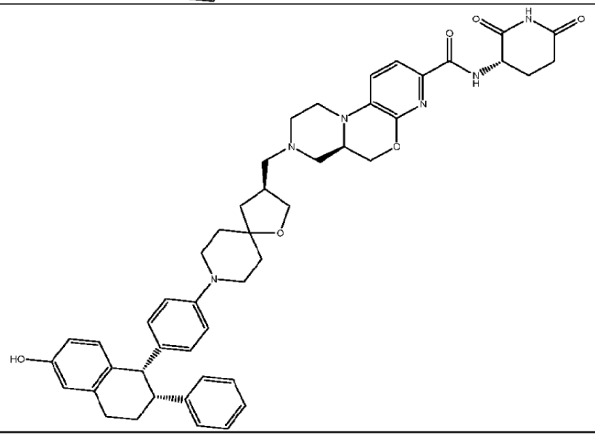
designates that it is enantiomerically pure with respect to the warhead (tetrahydronaphthalene) but the absolute configuration is not determined; the relative configuration of the two stereogenic centers is* ***cis**.*

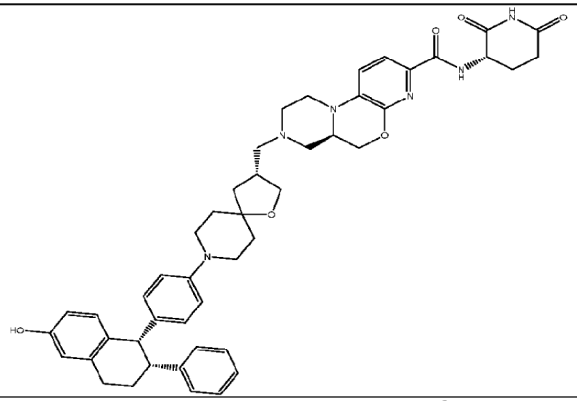
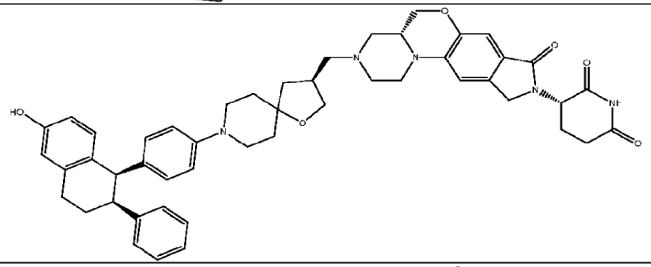
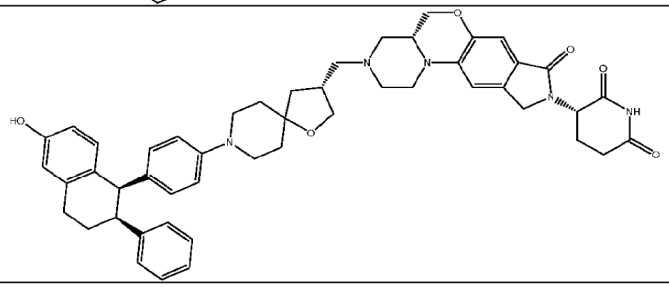
Compound No.	Structure	Compound Name
A1*		N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-6-methoxypicolinamide
A2		(4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A3		N-(2,6-dioxopiperidin-3-yl)-5-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)picolinamide

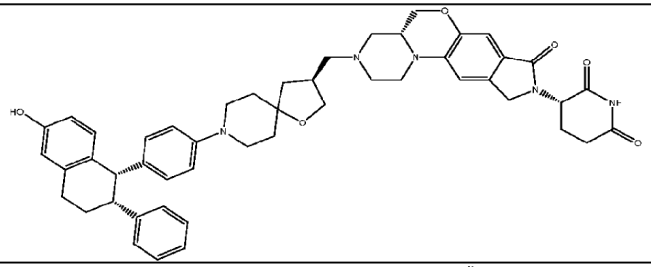
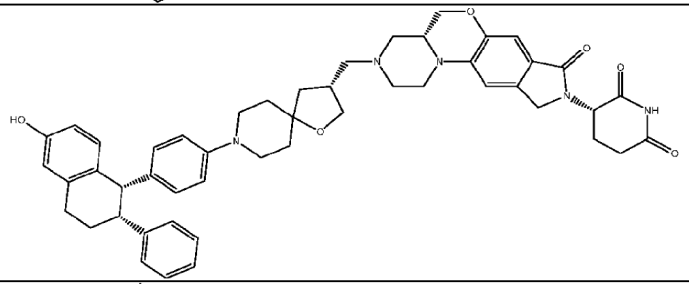
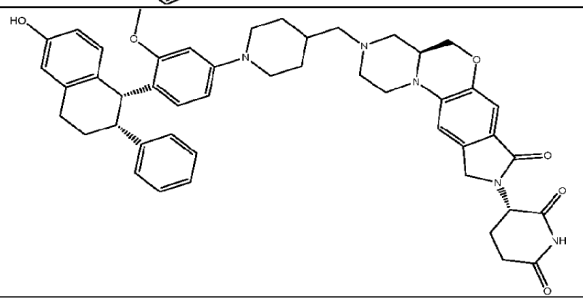
Compound No.	Structure	Compound Name
A4		(4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A5		N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide
A6*		(4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A7*		(3S)-3-((5aR)-7-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

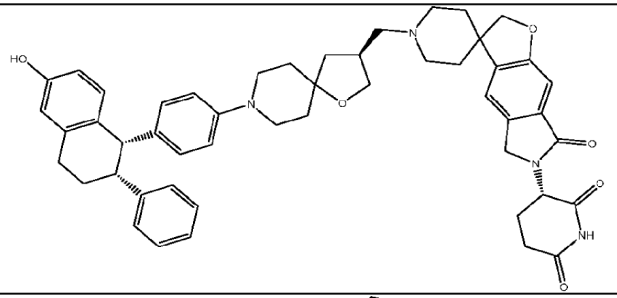
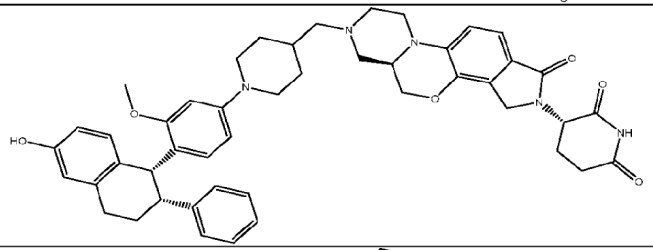
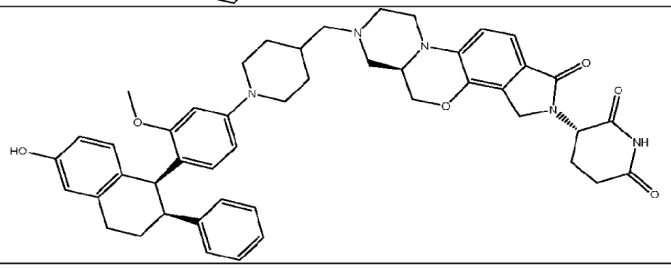
Compound No.	Structure	Compound Name
A8*		(S)-3-((S)-3-(((S)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]oCtan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A9*		(S)-3-((R)-7-((7-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-oCtahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A10*		(S)-3-((R)-7-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-oCtahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A11*		(S)-3-((S)-3-((7-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-oCtahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

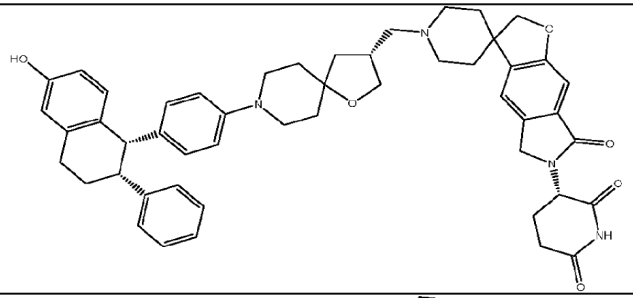
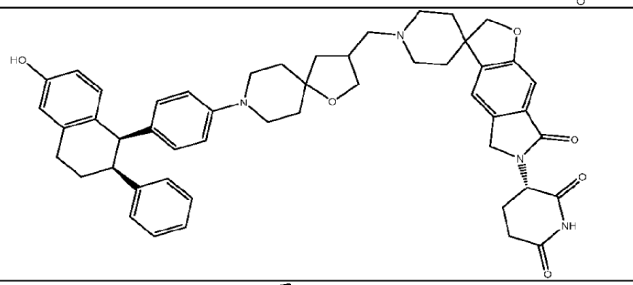
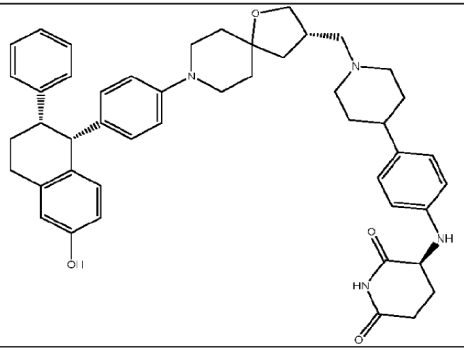
Compound No.	Structure	Compound Name
A12*		(S)-3-((S)-3-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-oCtahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A13*		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide

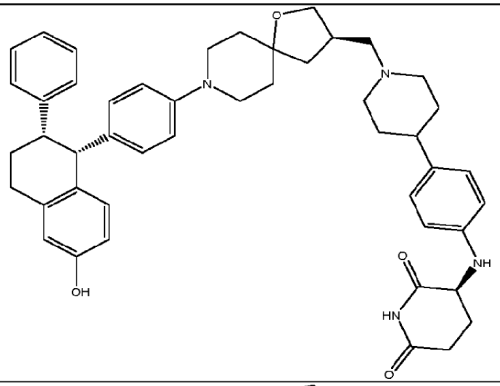
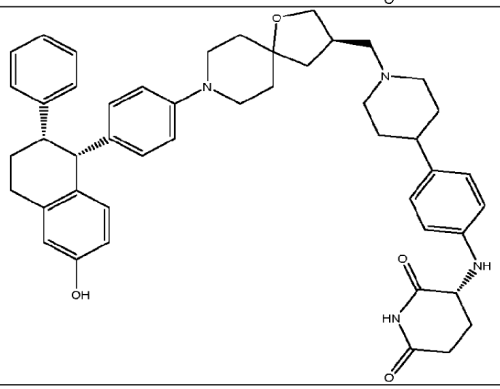
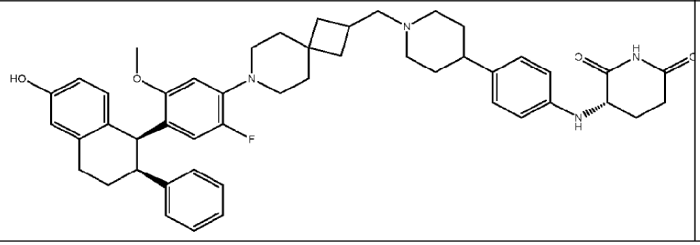
Compound No.	Structure	Compound Name
A14*		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A15*		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-(((S)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide

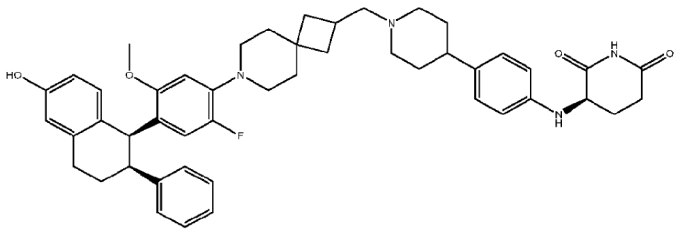
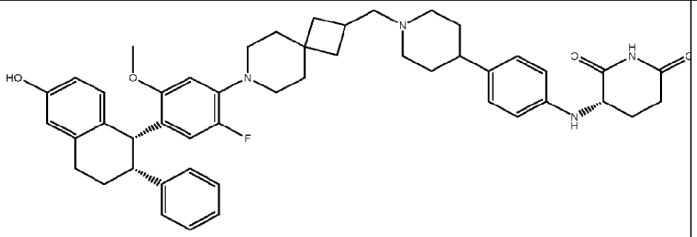
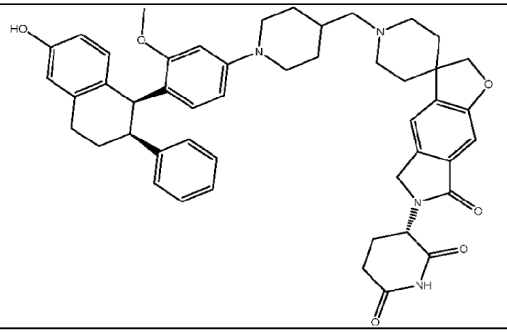
Compound No.	Structure	Compound Name
A16*		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-(((R)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A17*		(S)-3-((R)-3-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-oCtahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A18*		(S)-3-((R)-3-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-oCtahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

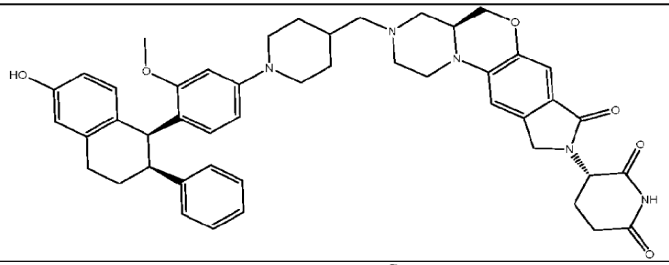
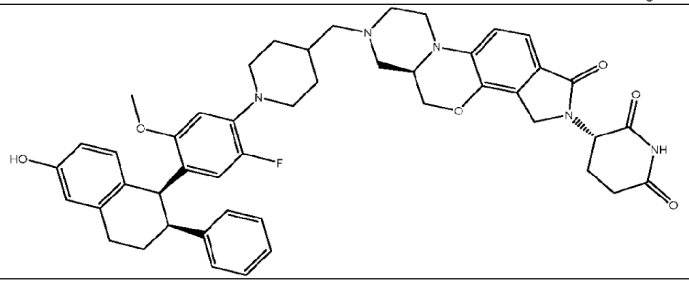
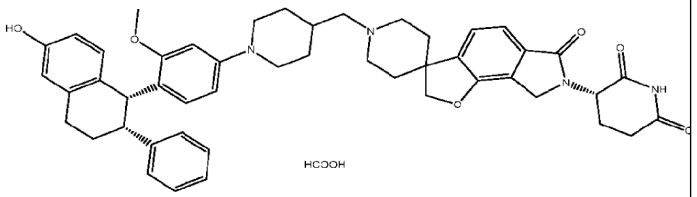
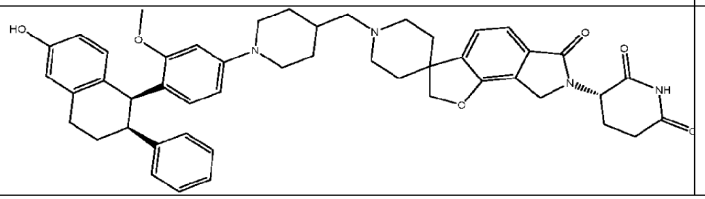
Compound No.	Structure	Compound Name
A19*		(S)-3-((R)-3-(((S)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-oCtahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A20*		(S)-3-((R)-3-(((R)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-oCtahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A21*		(S)-3-((S)-3-((1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-oCtahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

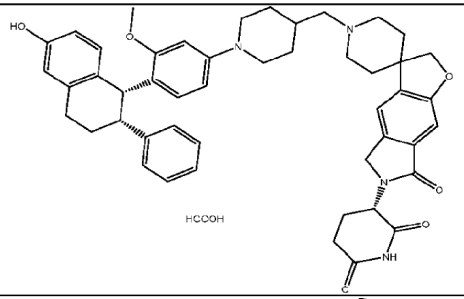
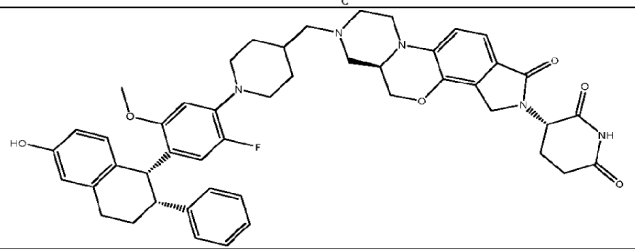
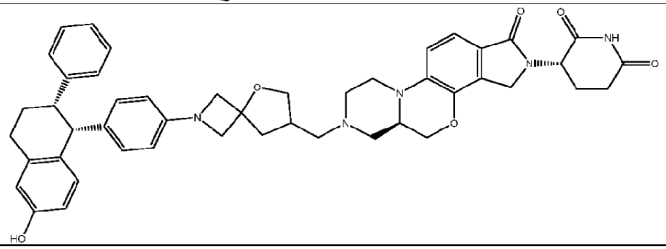
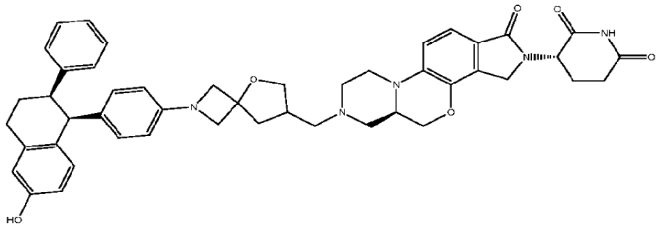
Compound No.	Structure	Compound Name
A22*		(S)-3-(1'-(((S)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A23*		(R)-3-((S)-7-((1-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-oCtahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A24*		(R)-3-((S)-7-((1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-oCtahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

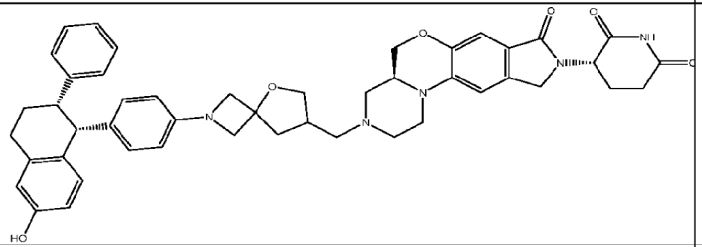
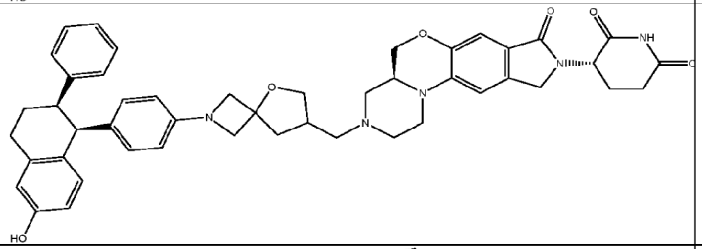
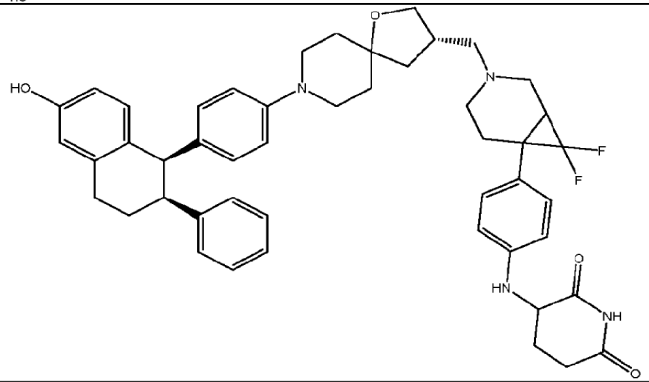
Compound No.	Structure	Compound Name
A25*		(3S)-3-((5aR)-7-((2-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-c]isoindol-2-yl)piperidine-2,6-dione
A26*		(3S)-3-(1'-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A27*		(R)-3-((4-(1-(((R)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione

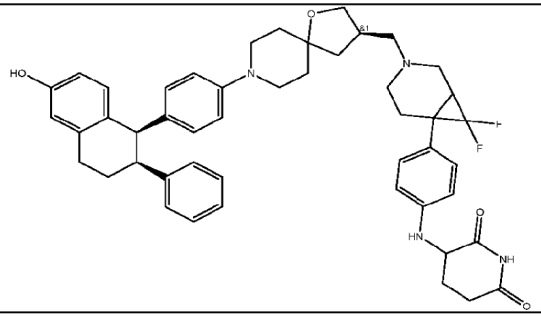
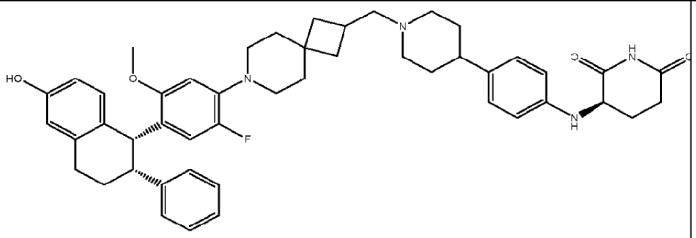
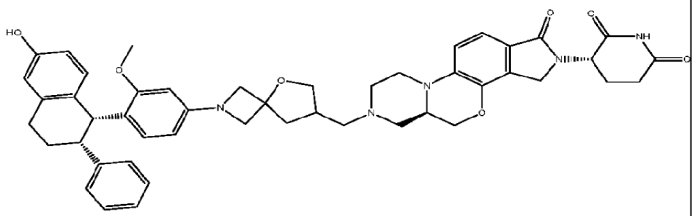
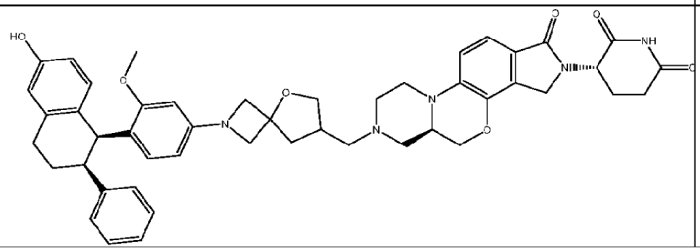
Compound No.	Structure	Compound Name
A28*		(R)-3-((4-(1-(((S)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A29*		(R)-3-((4-(1-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A30*		(S)-3-((4-(1-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione

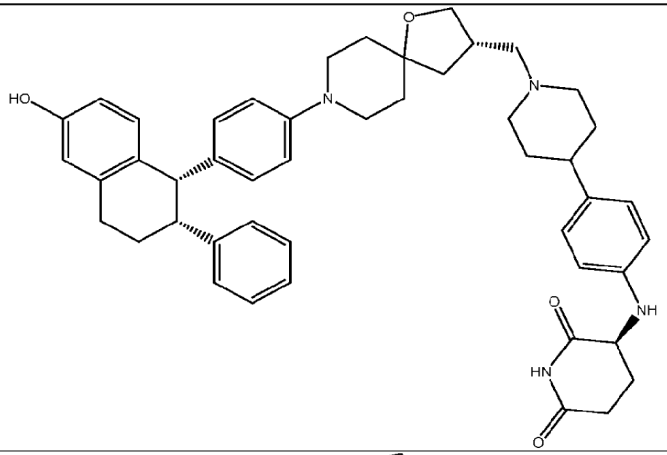
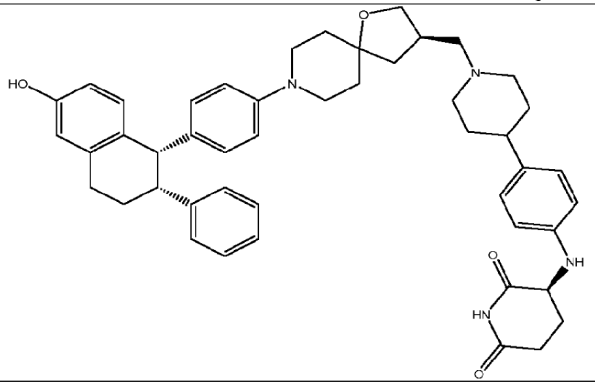
Compound No.	Structure	Compound Name
A31*		(R)-3-((4-(1-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A32*		(S)-3-((4-(1-((7-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A33*		(R)-3-(1'-((1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

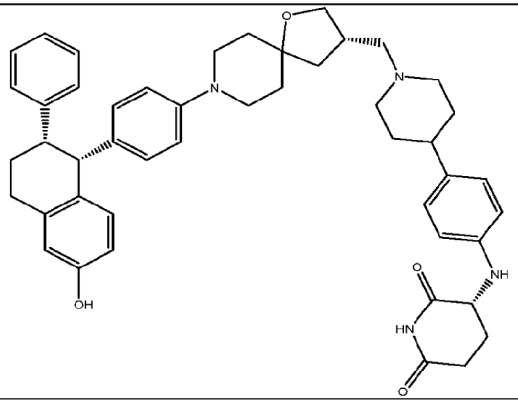
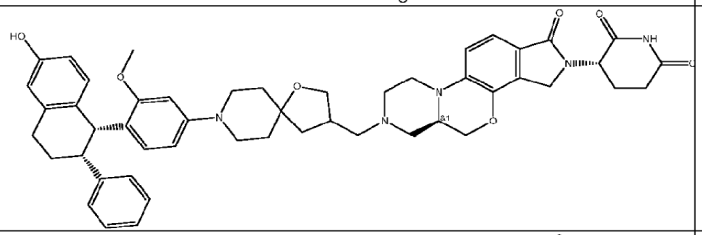
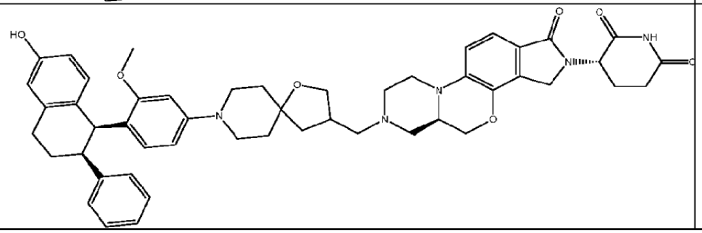
Compound No.	Structure	Compound Name
A34*		(S)-3-((S)-3-((1-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-oCtahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A35		(S)-3-((R)-7-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A36*		(R)-3-(1'-((1-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione formate
A37*		(R)-3-(1'-((1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

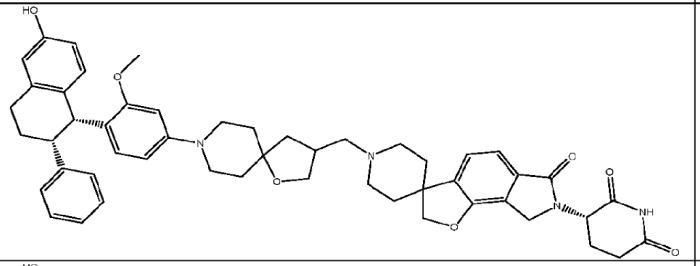
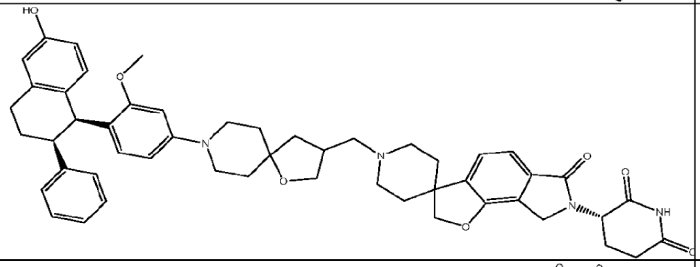
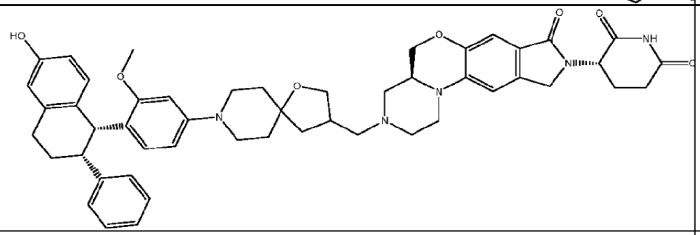
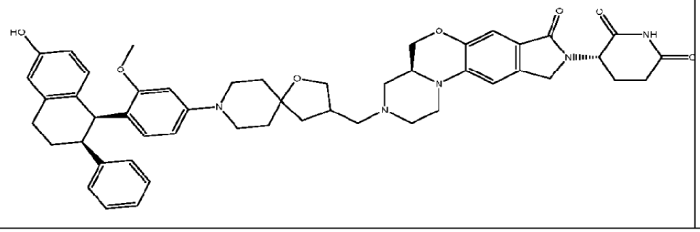
Compound No.	Structure	Compound Name
A38*		(R)-3-(1'-((1-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione formate
A39		(S)-3-((R)-7-((1-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A40*		(3S)-3-((5aR)-7-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A41*		(3S)-3-((5aR)-7-((2-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

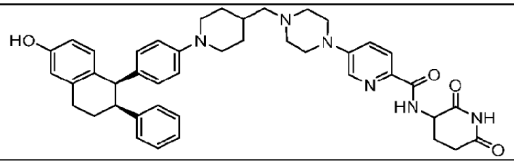
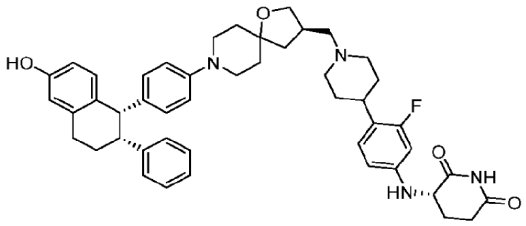
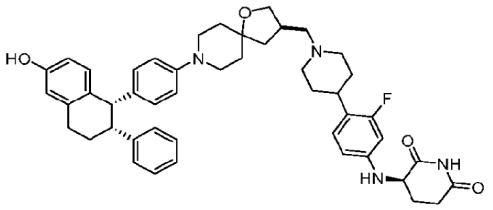
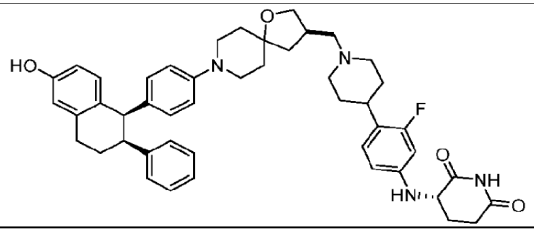
Compound No.	Structure	Compound Name
A42*		(3S)-3-((5aR)-7-((2-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A43*		(3S)-3-((4aS)-3-((2-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A44*		(3S)-3-((4-(7,7-difluoro-3-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione

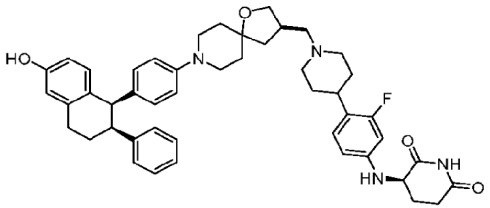
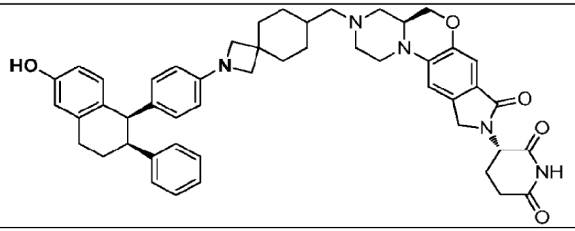
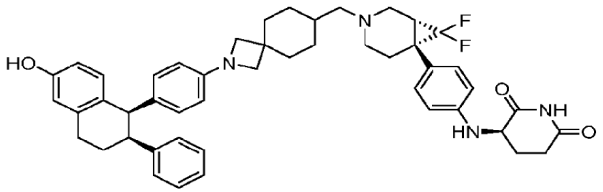
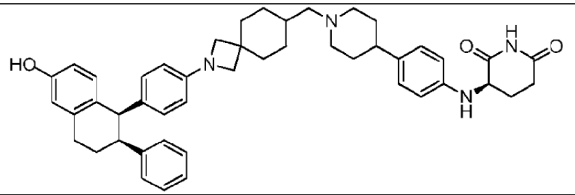
Compound No.	Structure	Compound Name
A45*		(3S)-3-((4-(7,7-difluoro-3-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione
A46*		(R)-3-((4-(1-((7-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A47*		(3S)-3-((5aR)-7-((2-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A48*		(3S)-3-((5aR)-7-((2-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

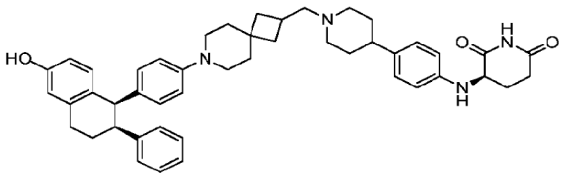
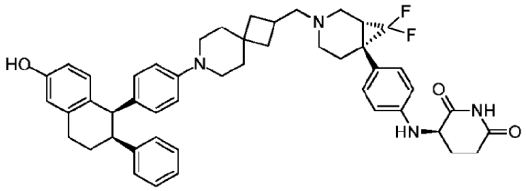
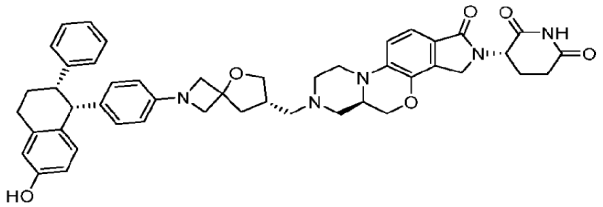
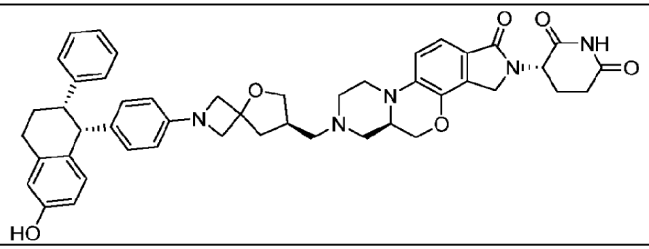
Compound No.	Structure	Compound Name
A49*		(S)-3-((4-(1-(((S)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A50*		(S)-3-((4-(1-(((R)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione

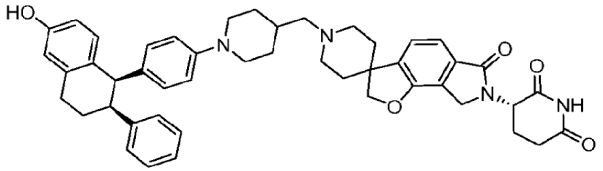
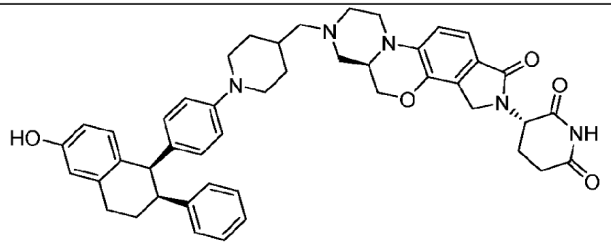
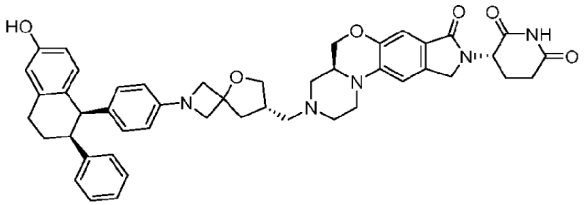
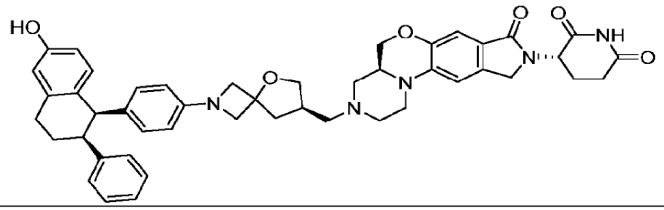
Compound No.	Structure	Compound Name
A51*		(R)-3-((4-(1-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A52*		(3S)-3-((5aRS)-7-((8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A53*		(3S)-3-((5aR)-7-((8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

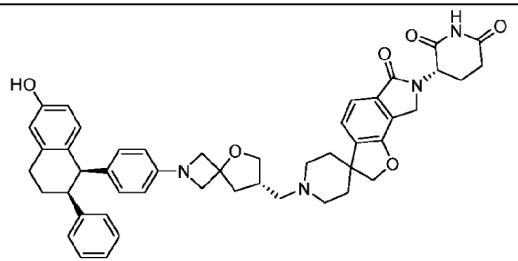
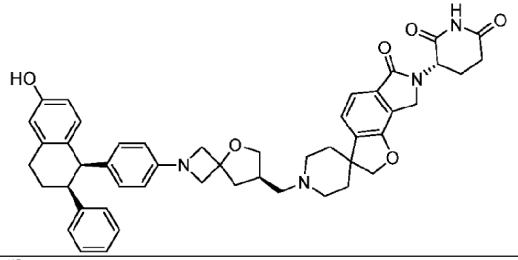
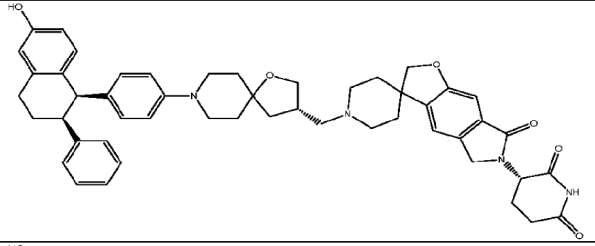
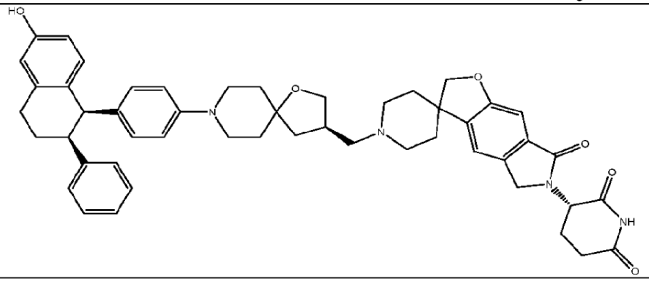
Compound No.	Structure	Compound Name
A54*		(3S)-3-(1'-((8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A55*		(3S)-3-(1'-((8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A56*		(3S)-3-((4aS)-3-((8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A57*		(3S)-3-((4aS)-3-((8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

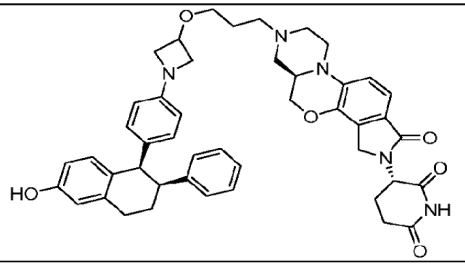
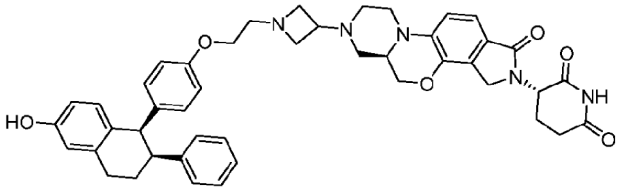
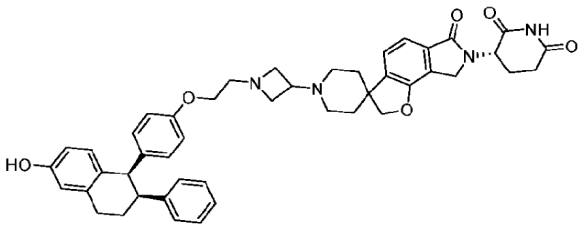
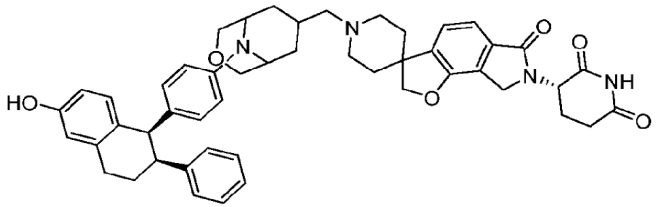
Compound No.	Structure	Compound Name
A58		N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide
A59*		(S)-3-((3-fluoro-4-(1-(((R)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A60*		(R)-3-((3-fluoro-4-(1-(((R)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A61*		(S)-3-((3-fluoro-4-(1-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione

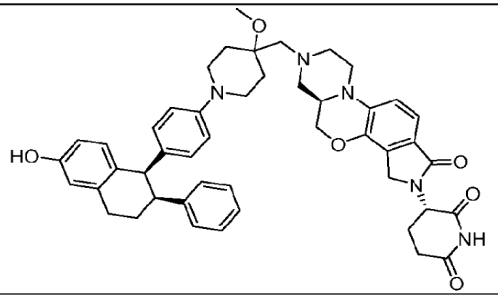
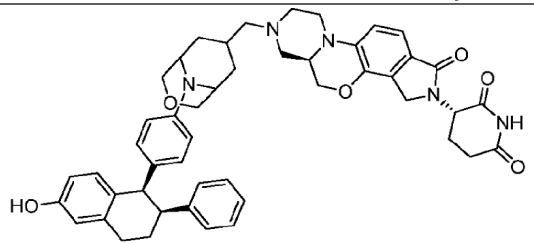
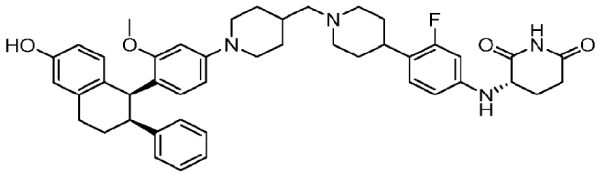
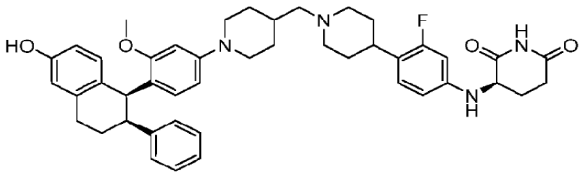
Compound No.	Structure	Compound Name
A62*		(R)-3-((3-fluoro-4-(1-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A63*		(S)-3-((S)-3-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-3,4,4a,5-tetrahydro-1H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9(2H,8H,10H)-yl)piperidine-2,6-dione
A64*		(R)-3-((4-((1R,6R)-7,7-difluoro-3-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione
A65*		(R)-3-((4-(1-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione

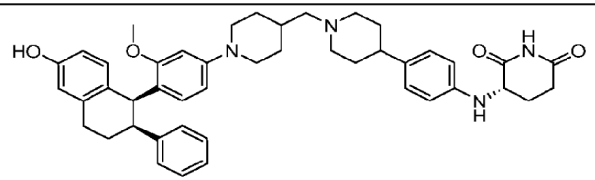
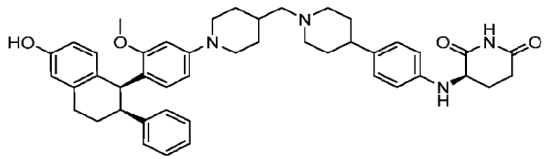
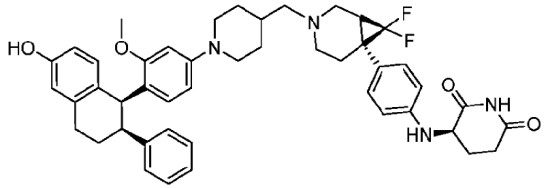
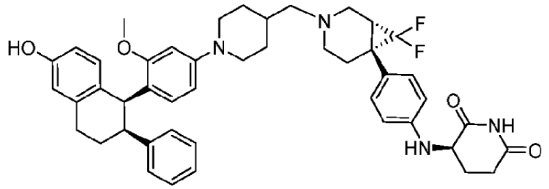
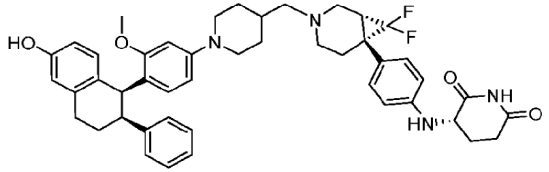
Compound No.	Structure	Compound Name
A66*		(R)-3-((4-(1-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A67*		(R)-3-((4-((1R,6R)-7,7-difluoro-3-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione
A68*		(S)-3-((R)-7-(((S)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A69*		(S)-3-((R)-7-(((R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

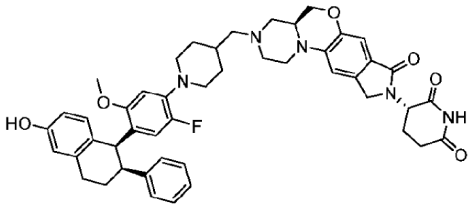
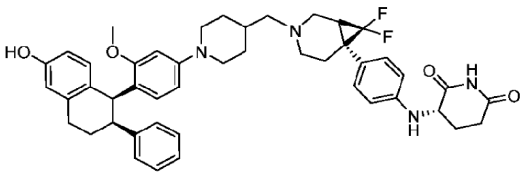
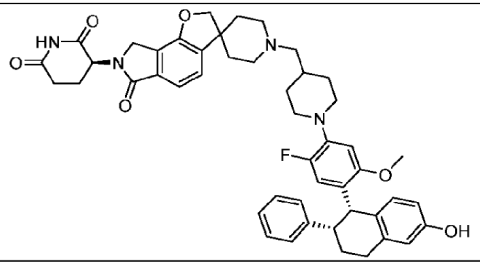
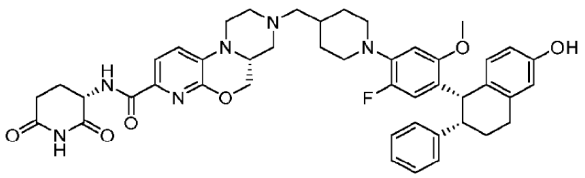
Compound No.	Structure	Compound Name
A70		(S)-3-(1'-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A71		(S)-3-((R)-7-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A72		(S)-3-((S)-3-(((S)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A73		(S)-3-((S)-3-(((R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

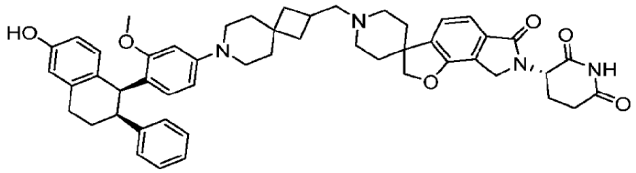
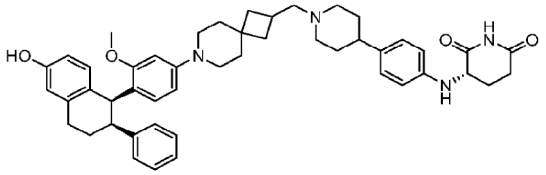
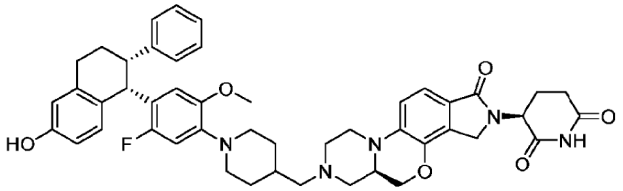
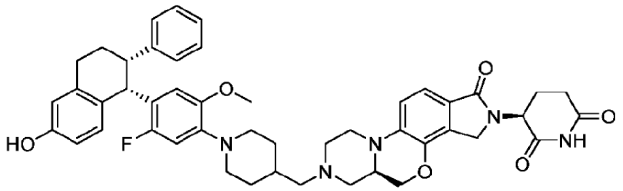
Compound No.	Structure	Compound Name
A74		(S)-3-(1'-(((S)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A75		(S)-3-(1'-(((R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A76		(S)-3-(1'-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A77		(S)-3-(1'-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

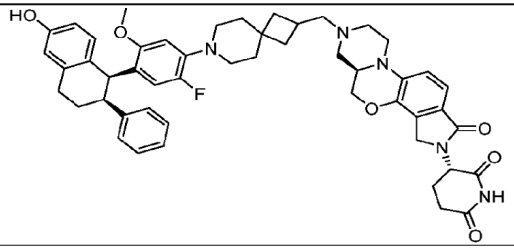
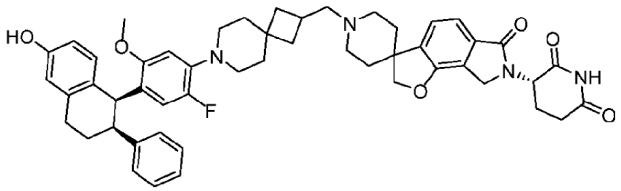
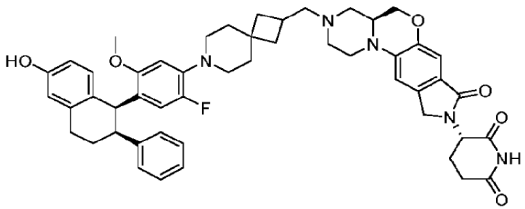
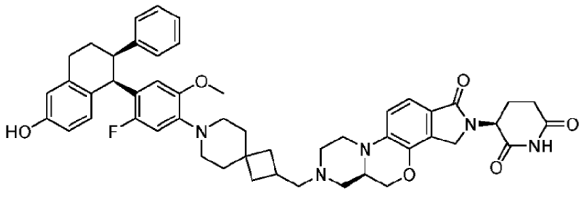
Compound No.	Structure	Compound Name
A78		(S)-3-((R)-7-(3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)oxy)propyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A79		(S)-3-((R)-7-(1-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)ethyl)azetidin-3-yl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A80		(S)-3-(1'-(1-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)ethyl)azetidin-3-yl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-c]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A81		(3S)-3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

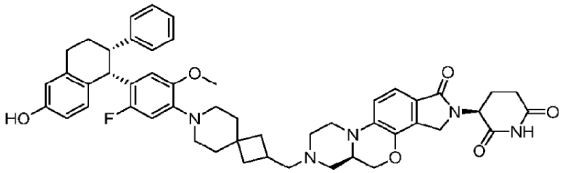
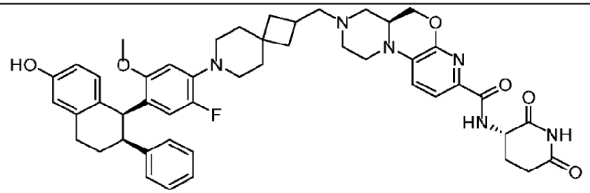
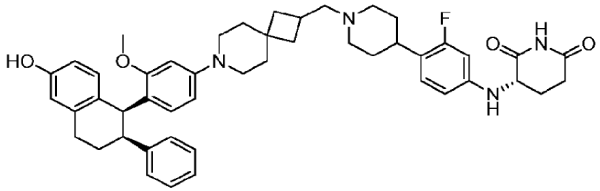
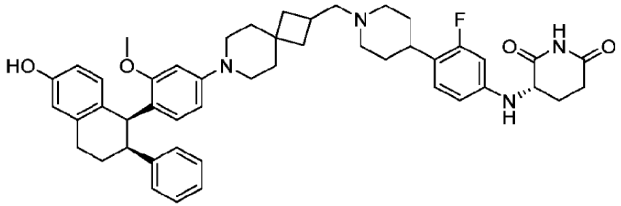
Compound No.	Structure	Compound Name
A82		(S)-3-((R)-7-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-4-methoxypiperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-c]isoindol-2-yl)piperidine-2,6-dione
A83		(3S)-3-((5aR)-7-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A84*		(R)-3-((3-fluoro-4-(1-((1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione formate
A85*		(R)-3-((3-fluoro-4-(1-((1-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione formate

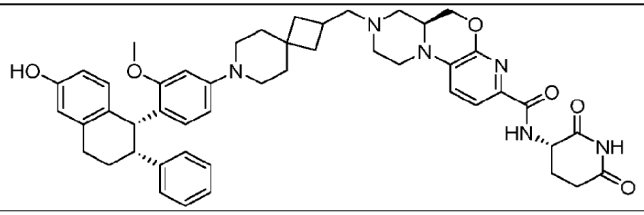
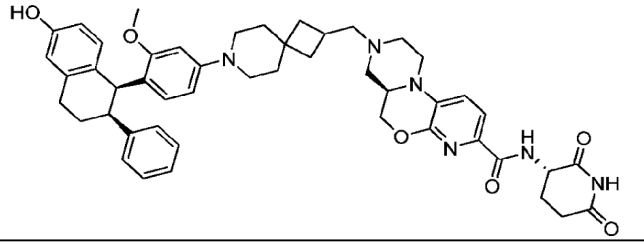
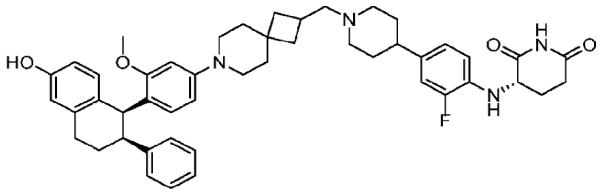
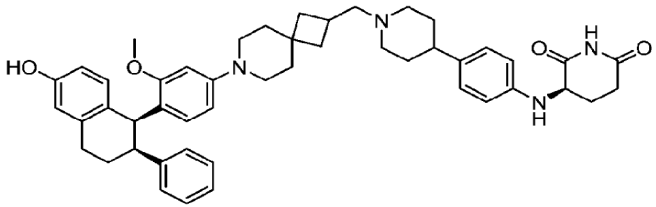
Compound No.	Structure	Compound Name
A86*		(R)-3-((4-(1-((1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A87*		(R)-3-((4-(1-((1-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A88*		(3R)-3-((4-((1R)-7,7-difluoro-3-((1-(4-((1SR,2SR)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione
A89*		(R)-3-((4-((1R,6R)-7,7-difluoro-3-((1-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione
A90*		(S)-3-((4-((1R,6R)-7,7-difluoro-3-((1-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione

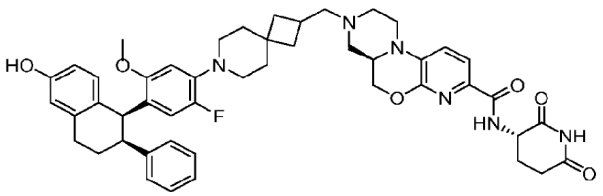
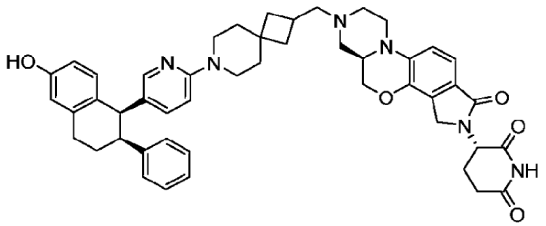
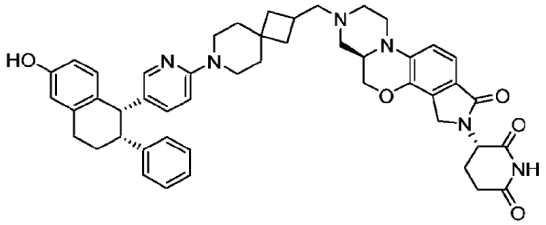
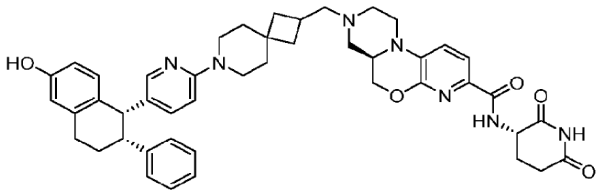
Compound No.	Structure	Compound Name
A91		(S)-3-((S)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A92*		(3S)-3-((4-((1R)-7,7-difluoro-3-((1-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione
A93		(S)-3-(1'-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A94		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide

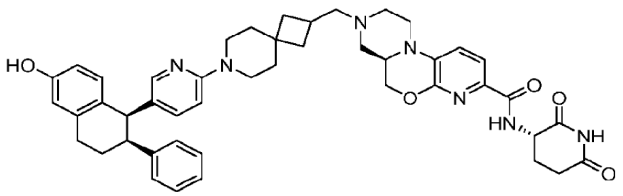
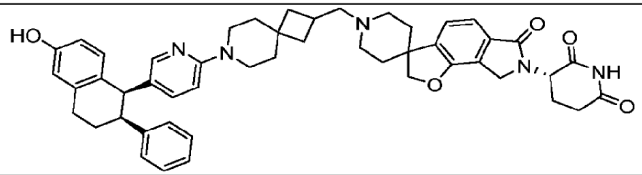
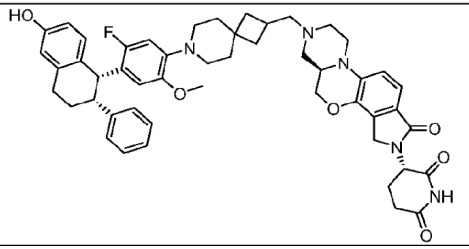
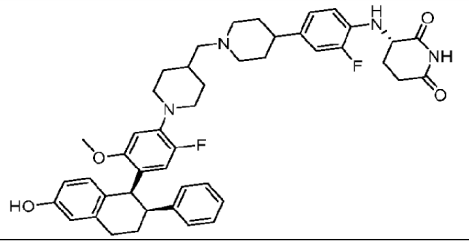
Compound No.	Structure	Compound Name
A95*		(S)-3-(1'-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A96*		(S)-3-((4-(1-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A97*		(S)-3-((R)-7-((1-(5-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A98*		(S)-3-((R)-7-((1-(5-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

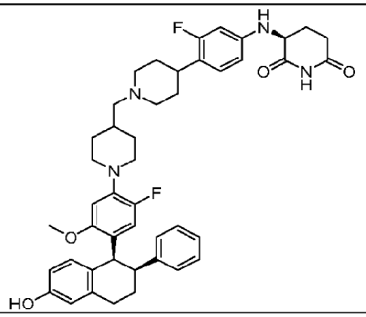
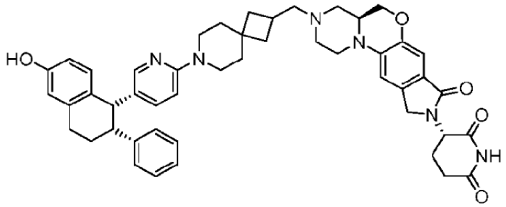
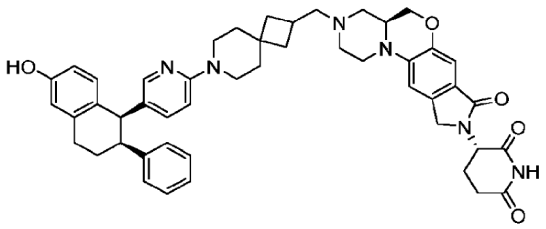
Compound No.	Structure	Compound Name
A99		(S)-3-((R)-7-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A100		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A101		(S)-3-((S)-3-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A102*		(S)-3-((R)-7-((7-(5-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

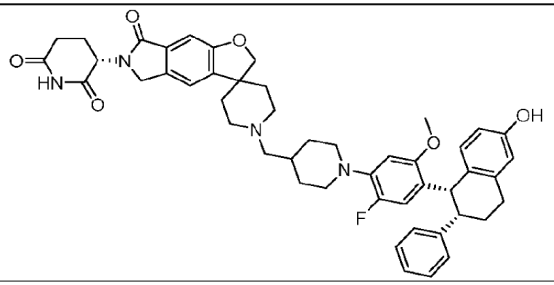
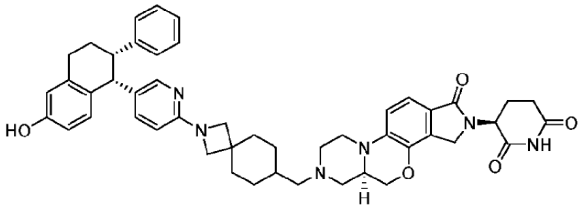
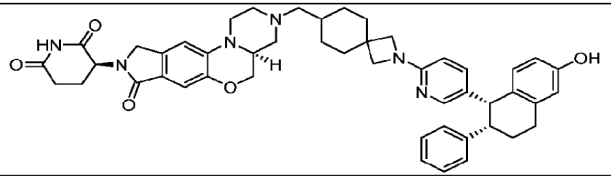
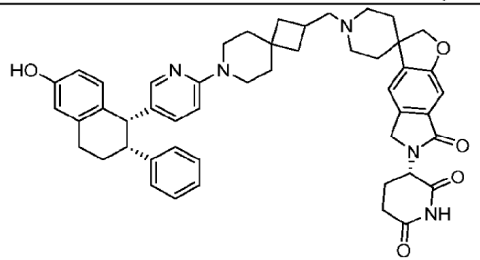
Compound No.	Structure	Compound Name
A103*		(S)-3-((R)-7-((7-(5-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A104		(S)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A105*		(S)-3-((3-fluoro-4-(1-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A106*		(R)-3-((3-fluoro-4-(1-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione

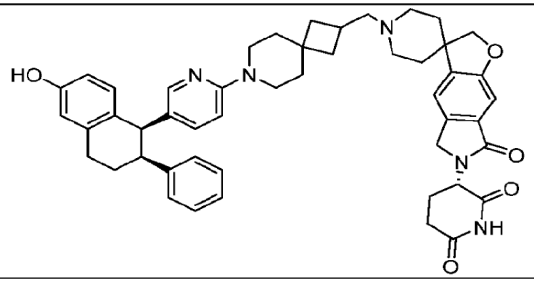
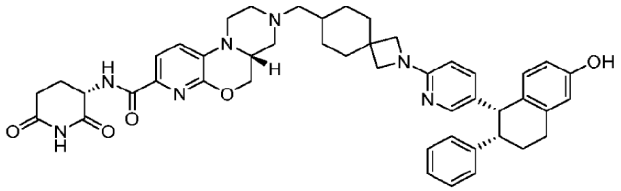
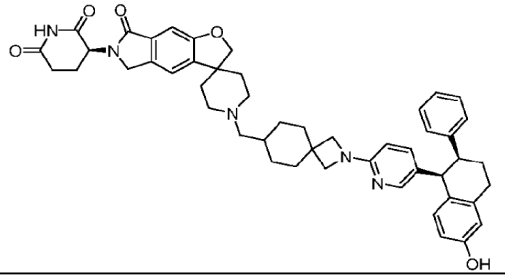
Compound No.	Structure	Compound Name
A107*		(S)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((7-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A108*		(S)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A109*		2-((S)-2,6-dioxopiperidin-3-yl)-5-(1-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)-3,5-dihydro-1H-pyrrolo[3,4-c]pyridine-1,4(2H)-dione
A110*		(R)-3-((4-(1-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione

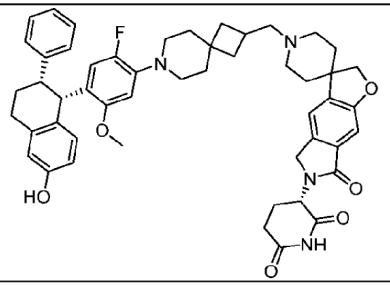
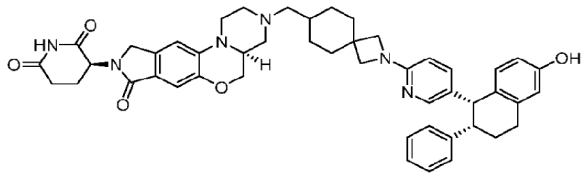
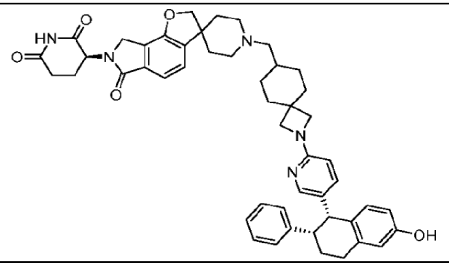
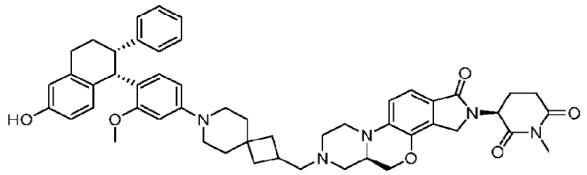
Compound No.	Structure	Compound Name
A111		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A112*		(S)-3-((R)-7-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A113*		(S)-3-((R)-7-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A114*		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide

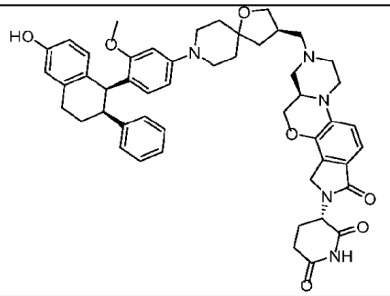
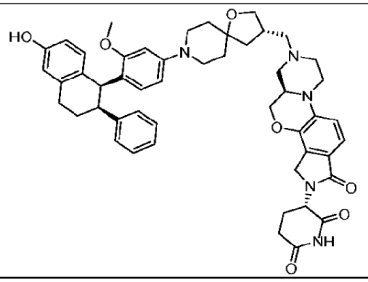
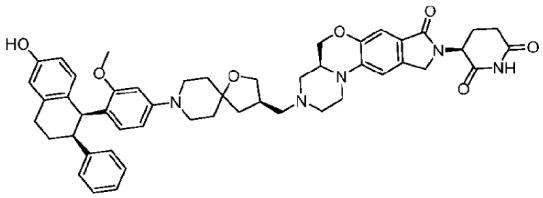
Compound No.	Structure	Compound Name
A115*		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A116*		(S)-3-(1'-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A117*		(S)-3-((R)-7-((7-(5-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A118		(S)-3-((2-fluoro-4-(1-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione

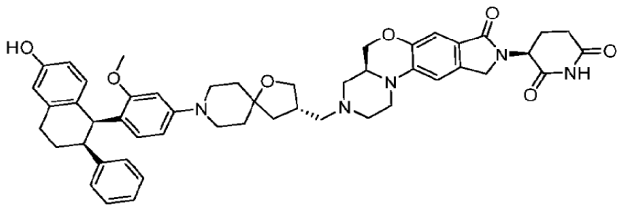
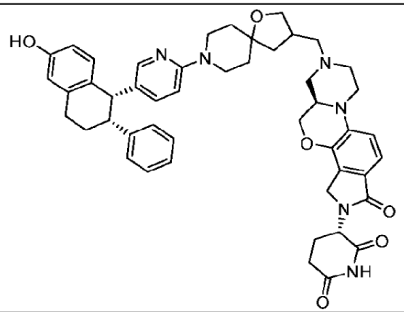
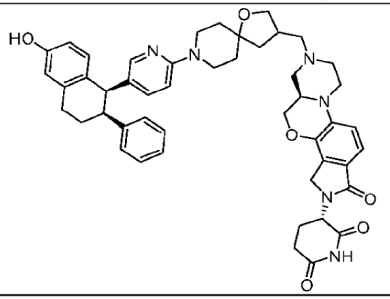
Compound No.	Structure	Compound Name
A119		(S)-3-((3-fluoro-4-(1-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A120*		(S)-3-((S)-3-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-3,4,4a,5-tetrahydro-1H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9(2H,8H,10H)-yl)piperidine-2,6-dione
A121*		(S)-3-((S)-3-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

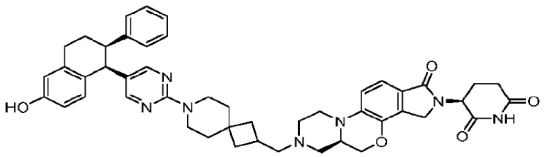
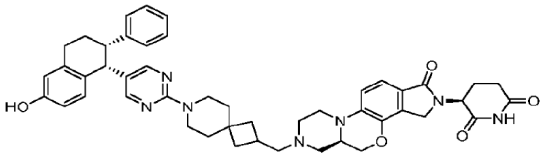
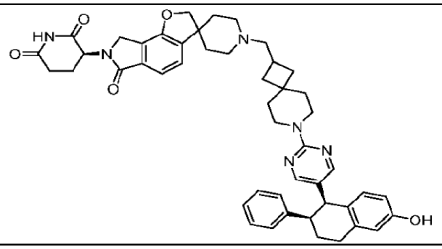
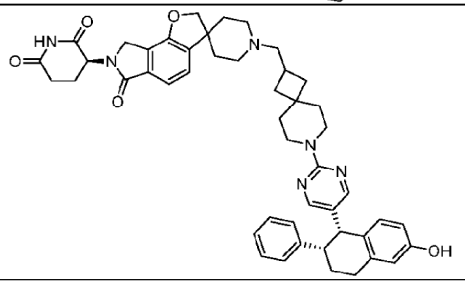
Compound No.	Structure	Compound Name
A122		(S)-3-(1'-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A123*		(S)-3-((R)-7-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A124*		(S)-3-((S)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A125*		(S)-3-(1'-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

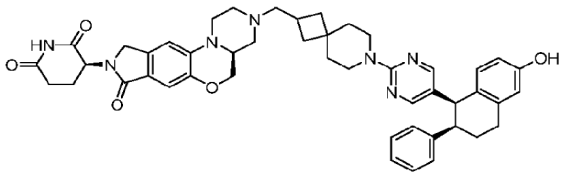
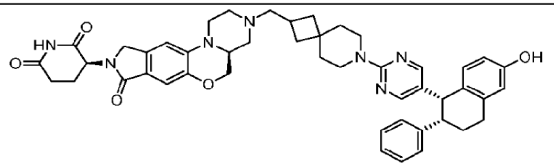
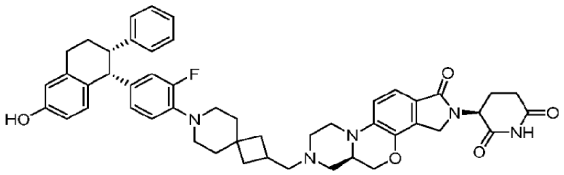
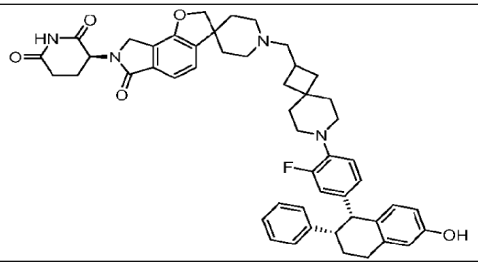
Compound No.	Structure	Compound Name
A126*		(S)-3-(1'-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A127*		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A128*		(S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

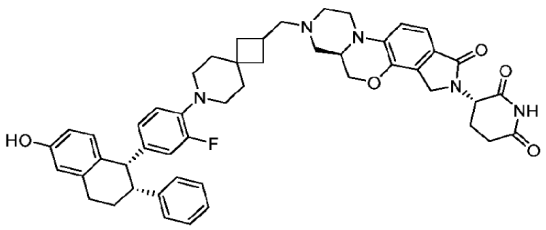
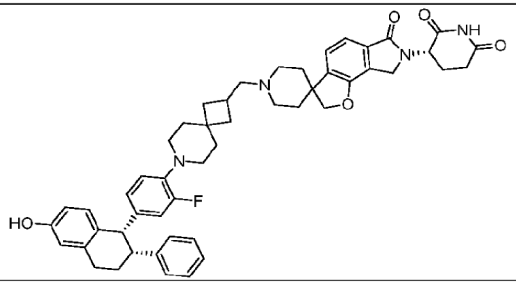
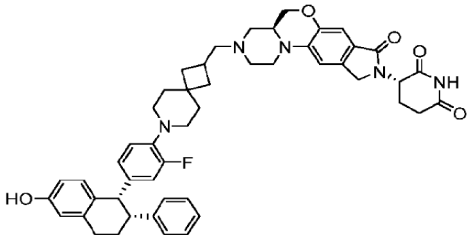
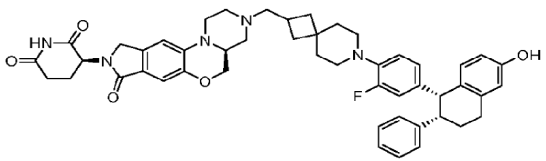
Compound No.	Structure	Compound Name
A129*		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A130*		(S)-3-((S)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A131*		(S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A132*		(S)-3-((R)-7-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)-1-methylpiperidine-2,6-dione

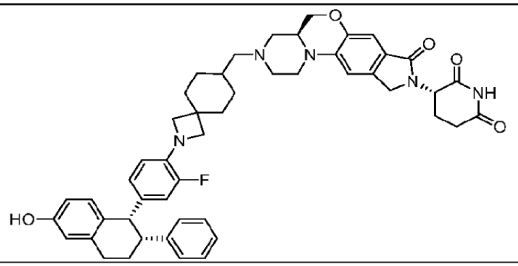
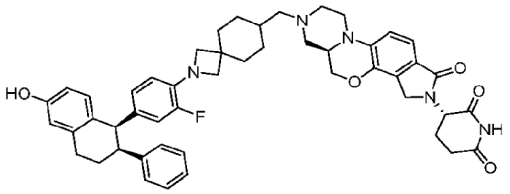
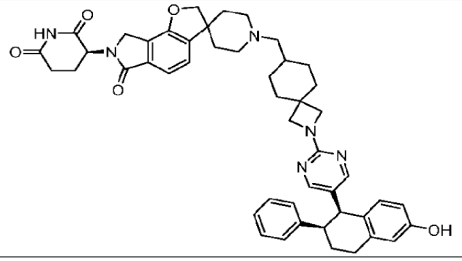
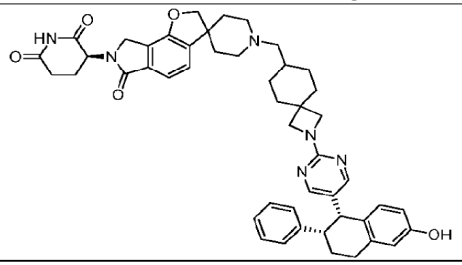
Compound No.	Structure	Compound Name
A133*		(S)-3-((R)-7-(((R)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A134*		(S)-3-((R)-7-(((S)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A135*		(S)-3-((S)-3-(((R)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

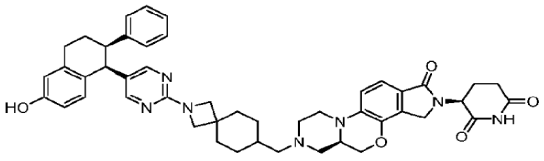
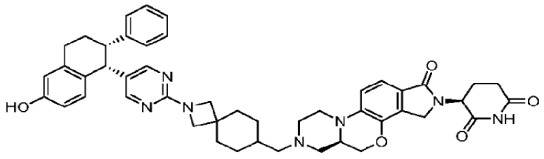
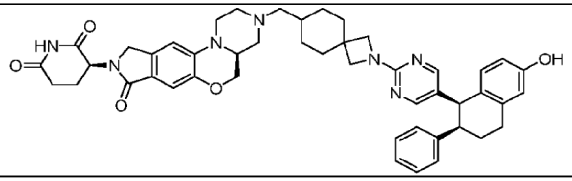
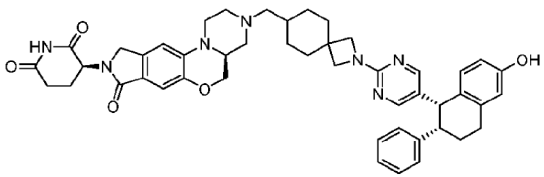
Compound No.	Structure	Compound Name
A136*		(S)-3-((S)-3-(((S)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A137*		(3S)-3-((5aR)-7-((8-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A138*		(3S)-3-((5aR)-7-((8-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

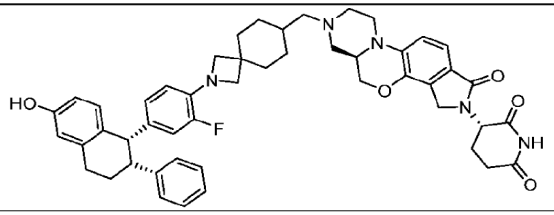
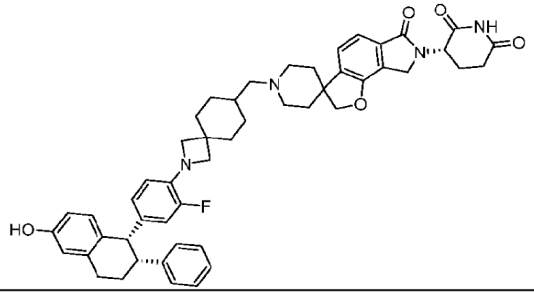
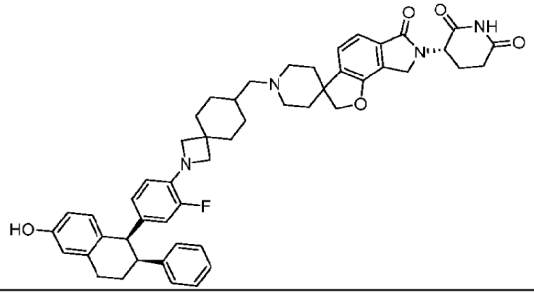
Compound No.	Structure	Compound Name
A139*		(S)-3-((R)-7-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A140*		(S)-3-((R)-7-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A141*		(S)-3-(1'-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-c]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A142*		(S)-3-(1'-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

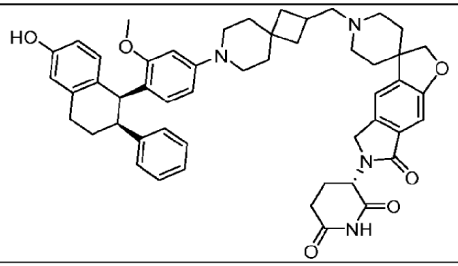
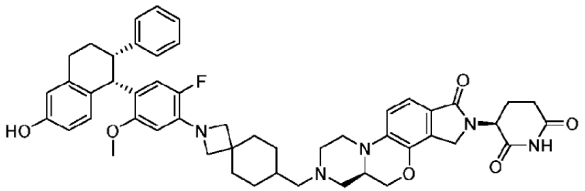
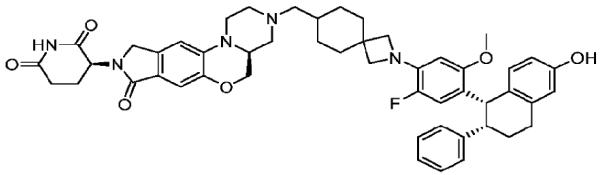
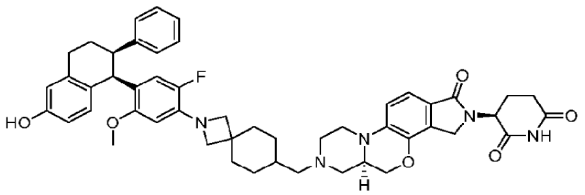
Compound No.	Structure	Compound Name
A143*		(S)-3-((S)-3-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A144*		(S)-3-((S)-3-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A145*		(S)-3-((R)-7-((7-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A146*		(S)-3-(1'-((7-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

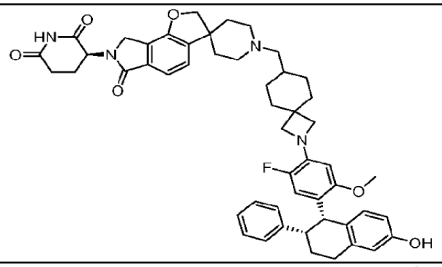
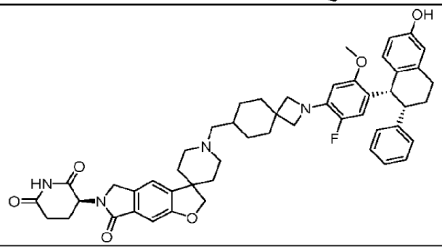
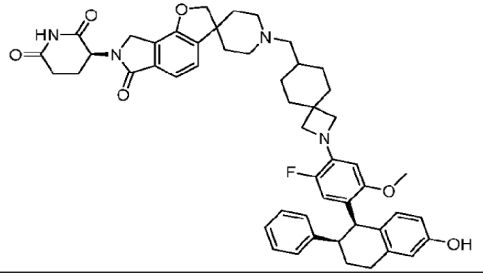
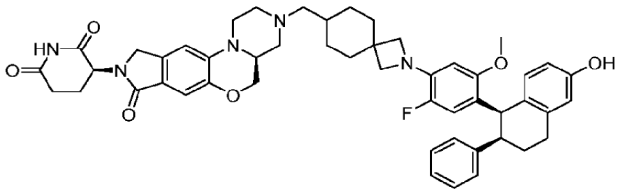
Compound No.	Structure	Compound Name
A147*		(S)-3-((R)-7-((7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A148*		(S)-3-(1'-((7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A149*		(S)-3-((S)-3-((7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A150*		(S)-3-((S)-3-((7-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

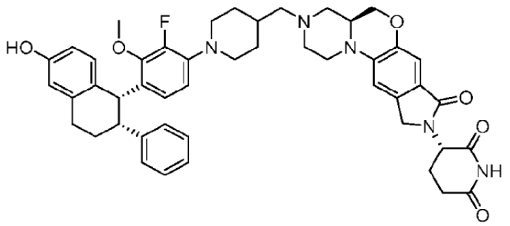
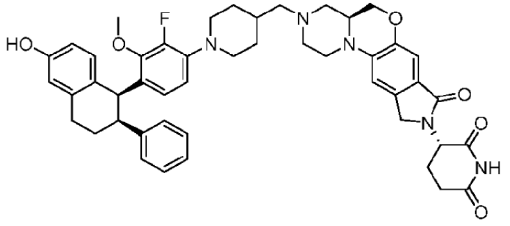
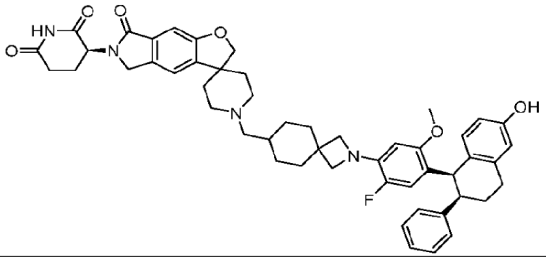
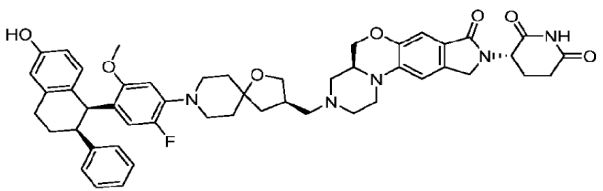
Compound No.	Structure	Compound Name
A151*		(S)-3-((S)-3-((2-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A152*		(S)-3-((R)-7-((2-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A153*		(S)-3-(1'-((2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A154*		(S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

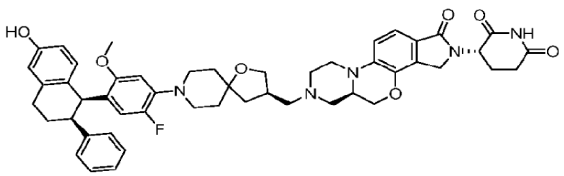
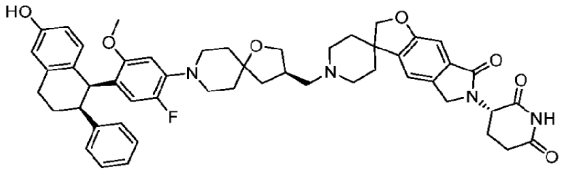
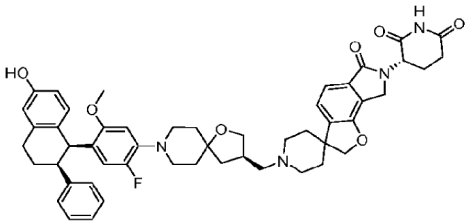
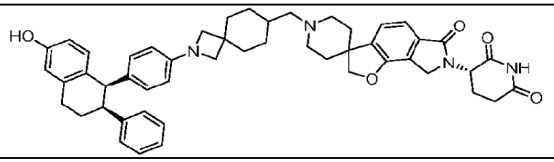
Compound No.	Structure	Compound Name
A155*		(S)-3-((R)-7-((2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A156*		(S)-3-((R)-7-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A157*		(S)-3-((S)-3-((2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A158*		(S)-3-((S)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

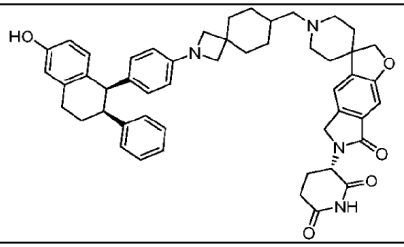
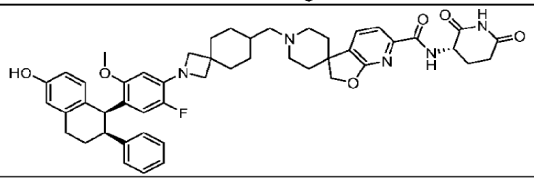
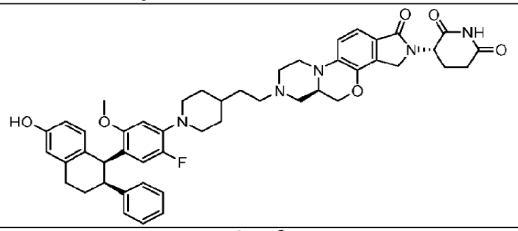
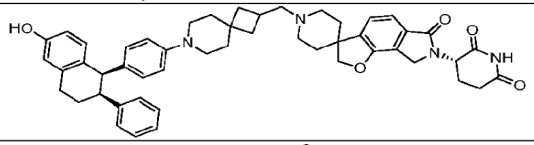
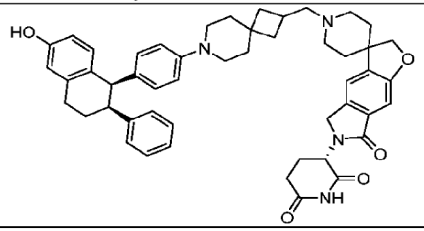
Compound No.	Structure	Compound Name
A159*		(S)-3-((R)-7-((2-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-5,5a,6,7,8,9-hexahydro-1H-pyrazino[1',2':4,5][1,4]oxazino[2,3-c]isoindol-2(3H)-yl)piperidine-2,6-dione
A160*		(S)-3-(1'-((2-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-c]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A161*		(S)-3-(1'-((2-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

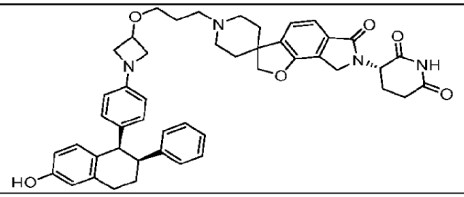
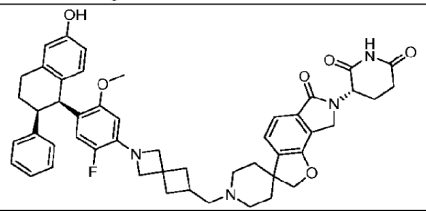
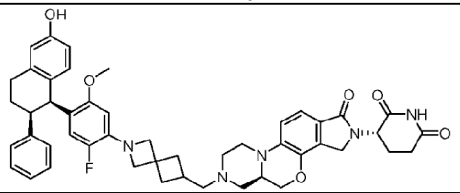
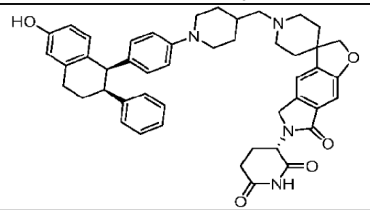
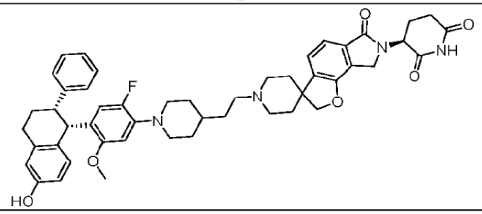
Compound No.	Structure	Compound Name
A162*		(S)-3-(1'-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A163*		(S)-3-((R)-7-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A164*		(S)-3-((S)-3-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A165*		(S)-3-((R)-7-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

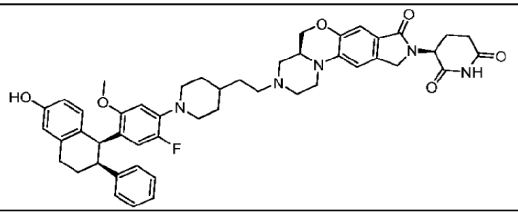
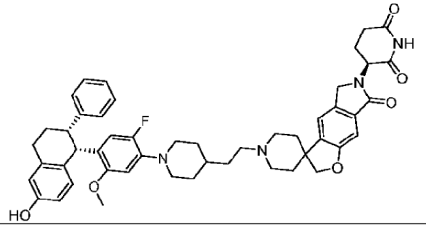
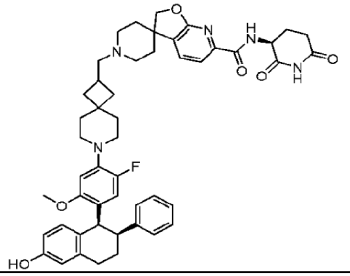
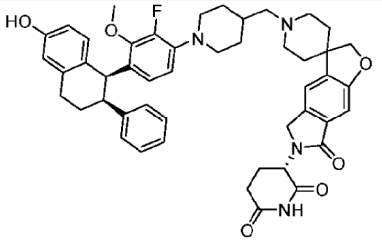
Compound No.	Structure	Compound Name
A166*		(S)-3-(1'-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A167*		(S)-3-(1'-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A168*		(S)-3-(1'-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A169*		(S)-3-((S)-3-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

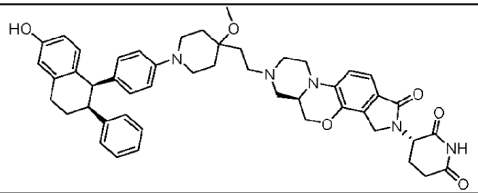
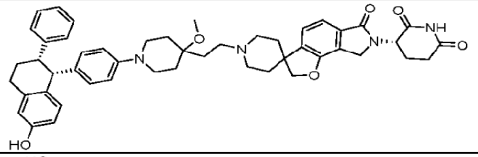
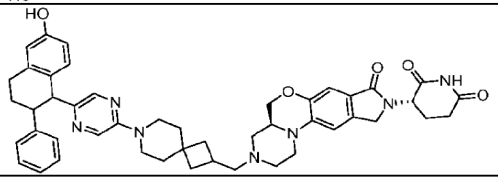
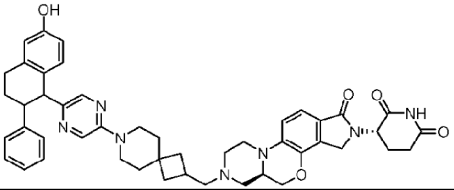
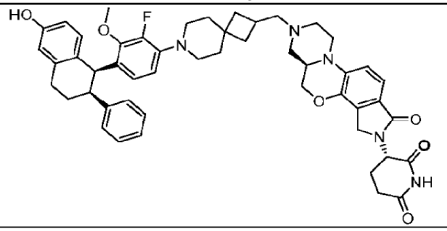
Compound No.	Structure	Compound Name
A170*		(S)-3-((S)-3-((1-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A171*		(S)-3-((S)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A172*		(S)-3-(1'-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A173		(S)-3-((S)-3-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

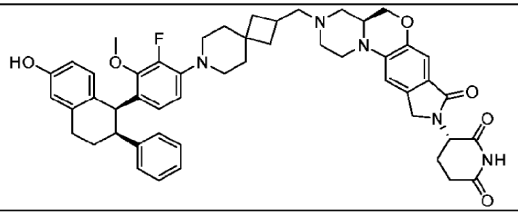
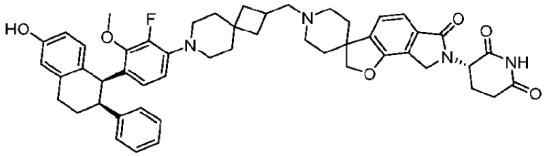
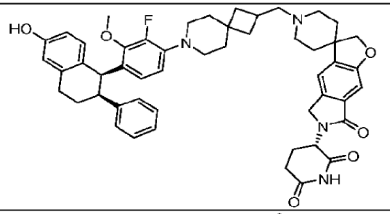
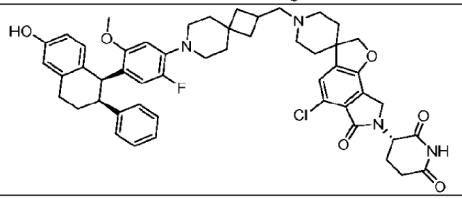
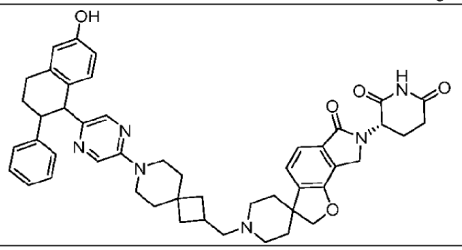
Compound No.	Structure	Compound Name
A174		(S)-3-((R)-7-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A175		(S)-3-(1'-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A176		(S)-3-(1'-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-c]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A177		(S)-3-(1'-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

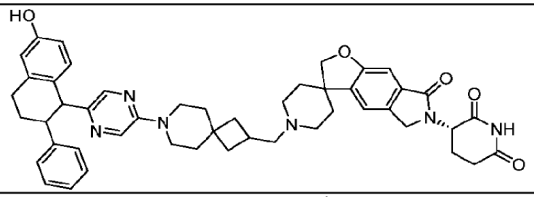
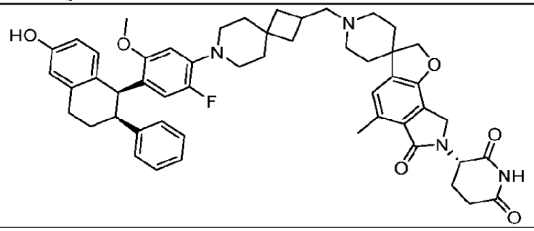
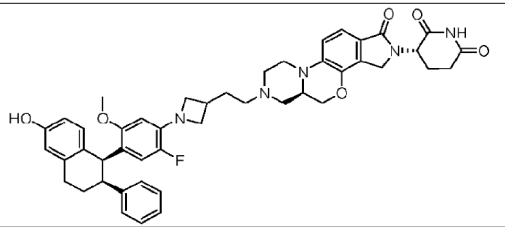
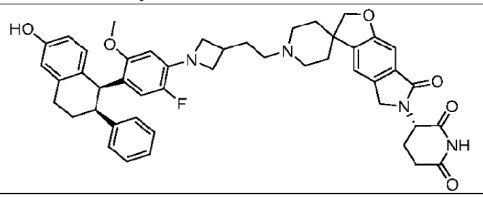
Compound No.	Structure	Compound Name
A178		(S)-3-(1'-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A179		N-((S)-2,6-dioxopiperidin-3-yl)-1'-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-2H-spiro[furo[2,3-b]pyridine-3,4'-piperidine]-6-carboxamide
A180		(S)-3-((R)-7-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A181		(S)-3-(1'-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A182		(S)-3-(1'-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

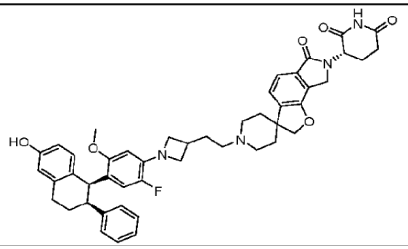
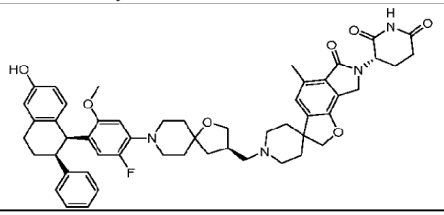
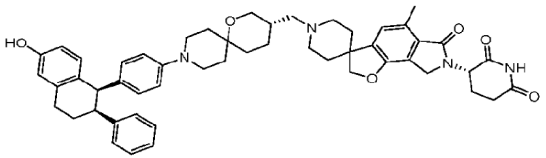
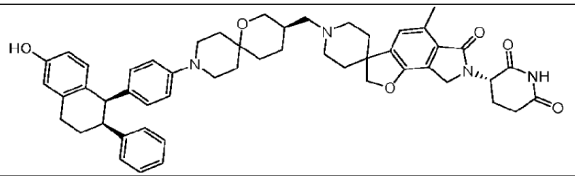
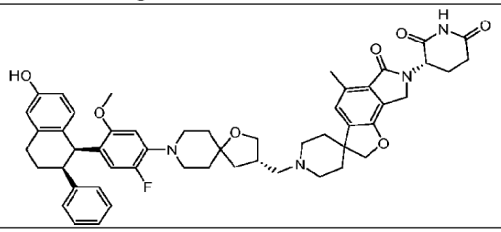
Compound No.	Structure	Compound Name
A183		(S)-3-(1'-(3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)oxy)propyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A184		(S)-3-(1'-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.3]heptan-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A185		(S)-3-((R)-7-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.3]heptan-6-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A186		(S)-3-(1'-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A187		(S)-3-(1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

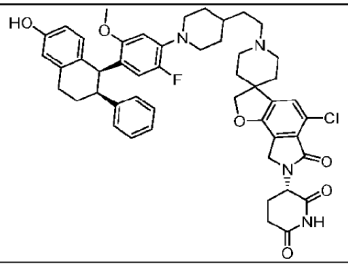
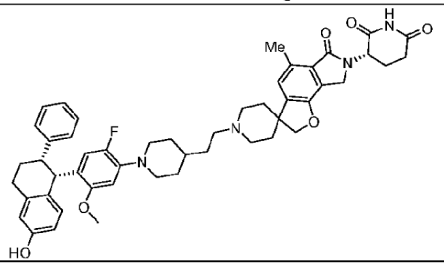
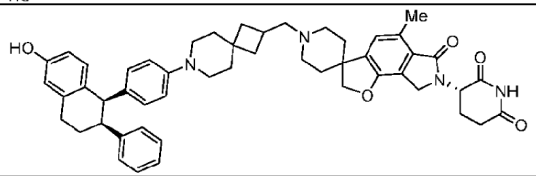
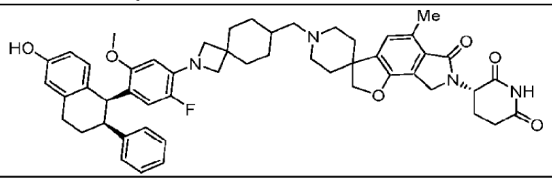
Compound No.	Structure	Compound Name
A188		(S)-3-((S)-3-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A189		(S)-3-(1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A190*		N-((S)-2,6-dioxopiperidin-3-yl)-1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-2H-spiro[furo[2,3-b]pyridine-3,4'-piperidine]-6-carboxamide
A191		(S)-3-(1'-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

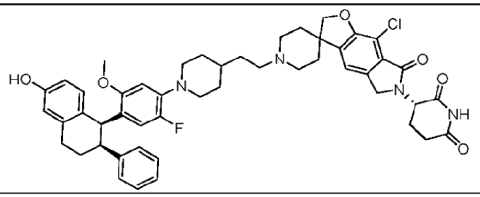
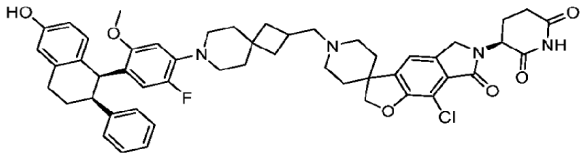
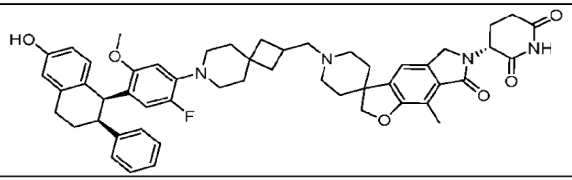
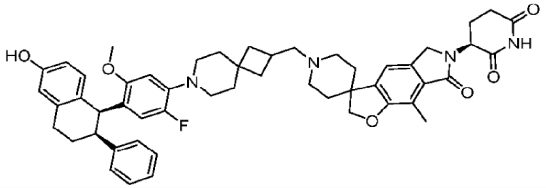
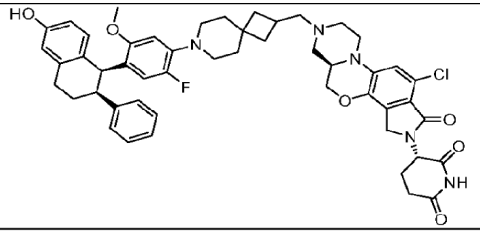
Compound No.	Structure	Compound Name
A192		(S)-3-((R)-7-(2-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-4-methoxypiperidin-4-yl)ethyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A193		(S)-3-(1'-(2-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-4-methoxypiperidin-4-yl)ethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A194		(3S)-3-((4aS)-3-((7-(5-(6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrazin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A195		(3S)-3-((5aR)-7-((7-(5-(6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrazin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A196		(S)-3-((R)-7-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

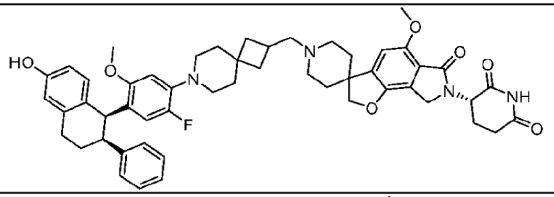
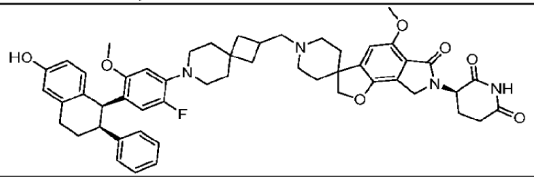
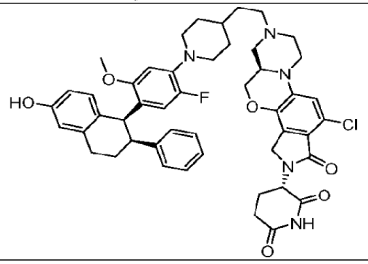
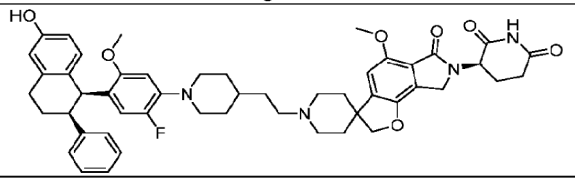
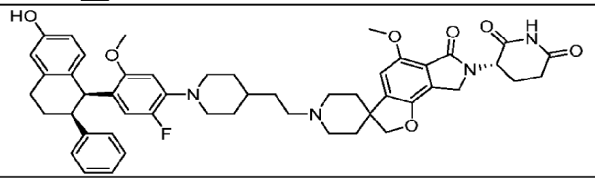
Compound No.	Structure	Compound Name
A197		(S)-3-((S)-3-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A198		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A199		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A200		(S)-3-(5-chloro-1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A201		(3S)-3-(1'-((7-(5-(6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrazin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

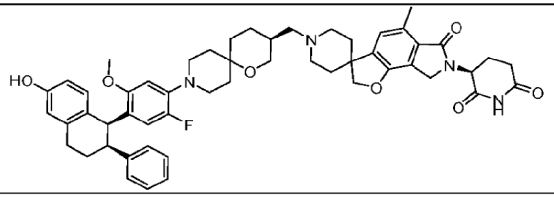
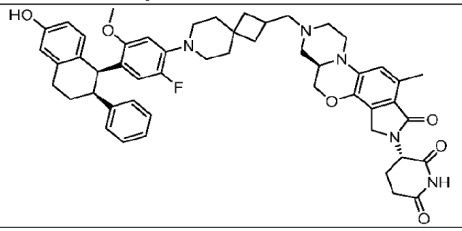
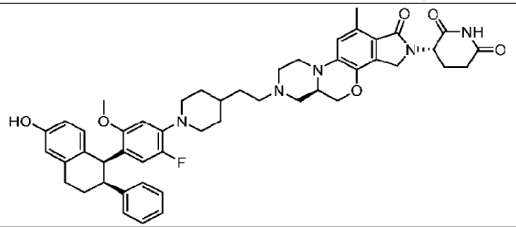
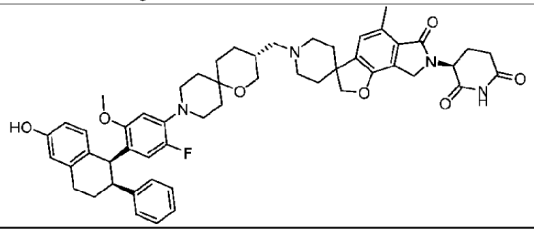
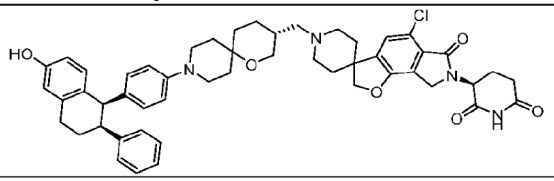
Compound No.	Structure	Compound Name
A202		(3S)-3-(1'-((7-(5-(6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrazin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A203		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A204		(S)-3-((R)-7-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)azetidin-3-yl)ethyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A205		(S)-3-(1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)azetidin-3-yl)ethyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

Compound No.	Structure	Compound Name
A206		(S)-3-(1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)azetidin-3-yl)ethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A208		(3S)-3-[1'-[[(3R)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione
A209		(S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A210		(S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A211		(3S)-3-[1'-[[(3S)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione

Compound No.	Structure	Compound Name
A212		(S)-3-(5-chloro-1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A213		(S)-3-(1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A214		(S)-3-(1'-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-c]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A216		(S)-3-(1'-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Structure	Compound Name
A217		(S)-3-(8-chloro-1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A218		(S)-3-(8-chloro-1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A219		(R)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-methyl-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A220		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-methyl-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A221		(S)-3-((R)-12-chloro-7-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

Compound No.	Structure	Compound Name
A222		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A223		(R)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A224		(S)-3-((R)-12-chloro-7-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A225		(R)-3-(1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A226		(S)-3-(1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Structure	Compound Name
A227		(S)-3-(1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A228		(S)-3-((R)-7-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-12-methyl-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A229		(S)-3-((R)-7-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-12-methyl-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A230		(S)-3-(1'-(((R)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A231		(S)-3-(5-chloro-1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

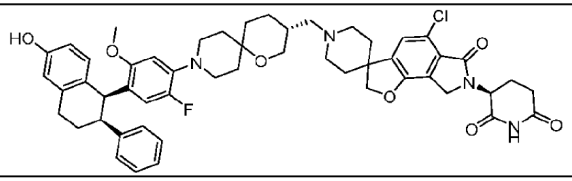
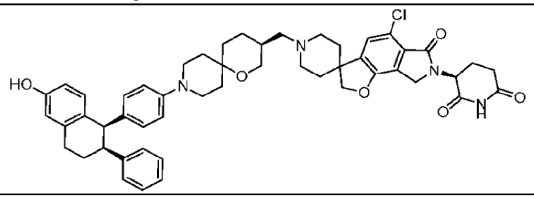
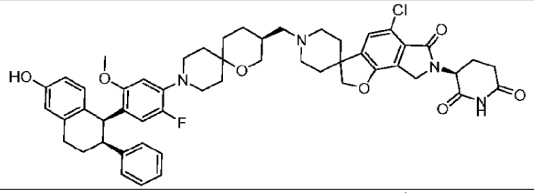
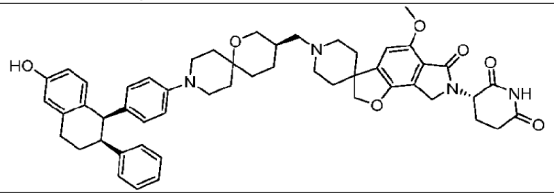
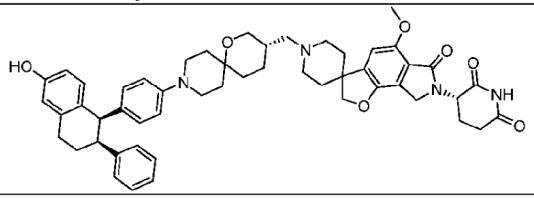
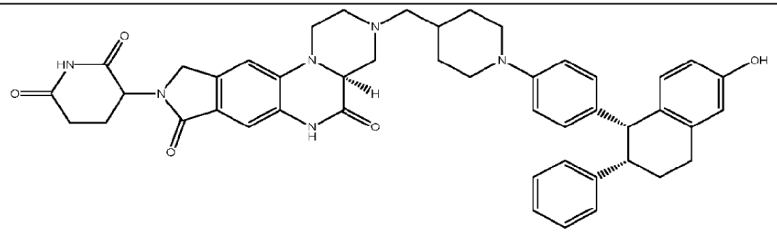
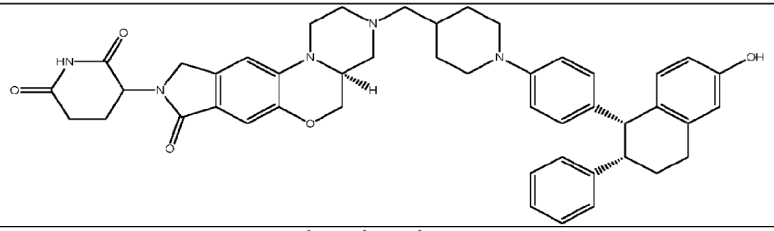
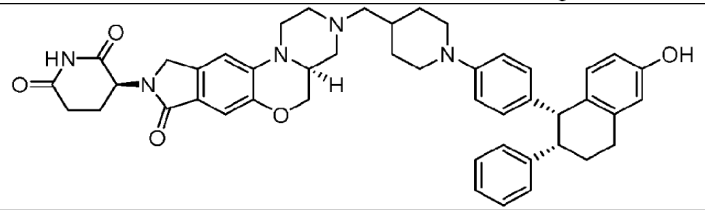
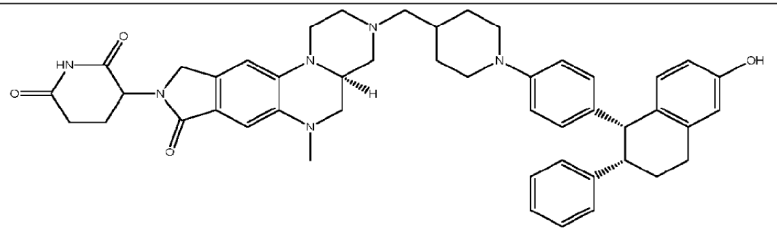
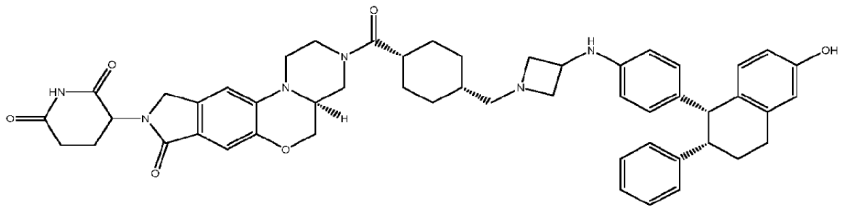
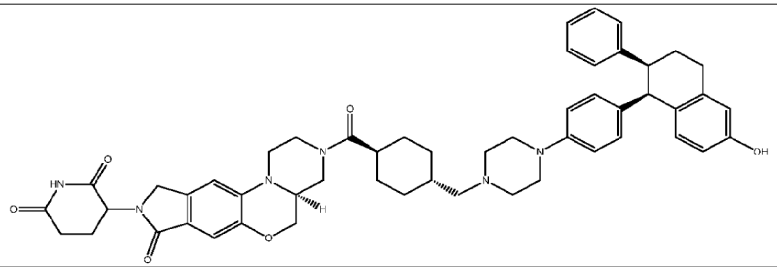
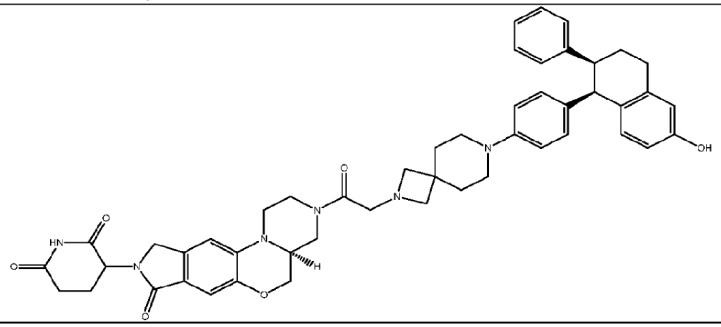
Compound No.	Structure	Compound Name
A232		(S)-3-(5-chloro-1'-(((R)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A233		(S)-3-(5-chloro-1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A234		(S)-3-(5-chloro-1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A235		(S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A236		(S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Table 2.

designates that it is racemic with respect to the two stereogenic centers at the warhead (tetrahydronaphthalene); the relative configuration of the two stereogenic center is **cis.*

Compound No.	Chemical Structure	Chemical Name
B134		(4aS)-9-(2,6-dioxopiperidin-3-yl)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-2,3,4,4a,9,10-hexahydropyrazino[1,2-a]pyrrolo[3,4-g]quinoxaline-5,8(1H,6H)-dione
B135		3-((S)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B135X		(S)-3-((S)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B137		3-((S)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-6-methyl-8-oxo-2,3,4,4a,5,6,8,10-octahydropyrazino[1,2-a]pyrrolo[3,4-g]quinoxalin-9(1H)-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B140		3-((S)-3-((1R,4S)-4-((3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)methyl)cyclohexane-1-carbonyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B141		3-((S)-3-((1R,4S)-4-((4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)methyl)cyclohexane-1-carbonyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B142		3-((S)-3-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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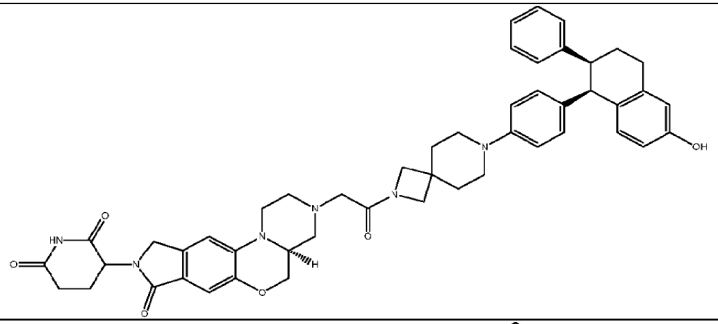
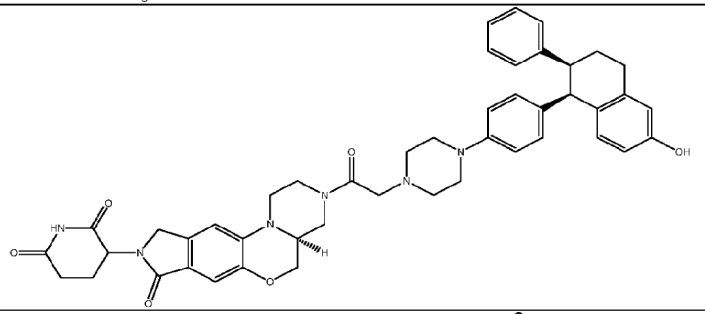
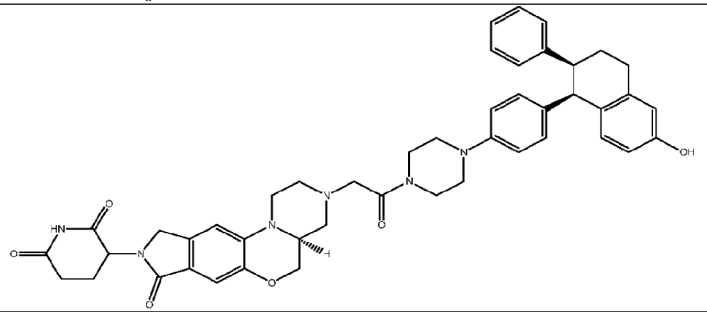
Compound No.	Chemical Structure	Chemical Name
B143		3-((S)-3-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B144		3-((S)-3-(2-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B145		3-((S)-3-(2-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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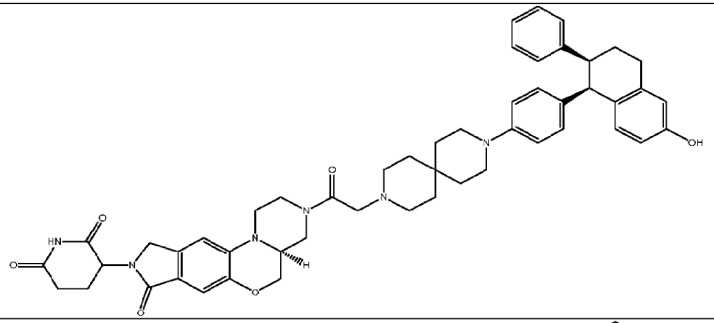
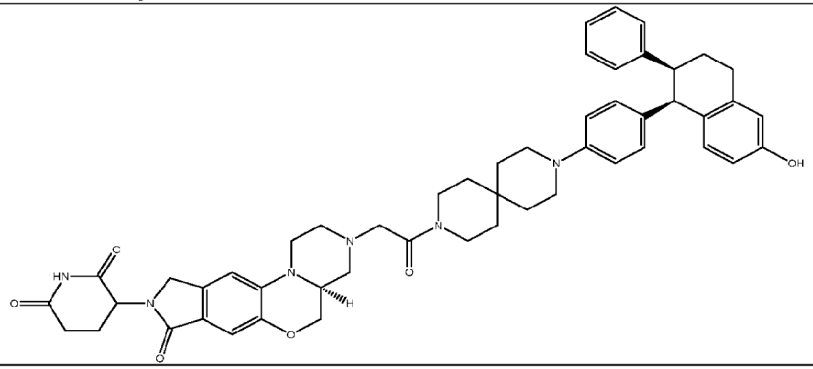
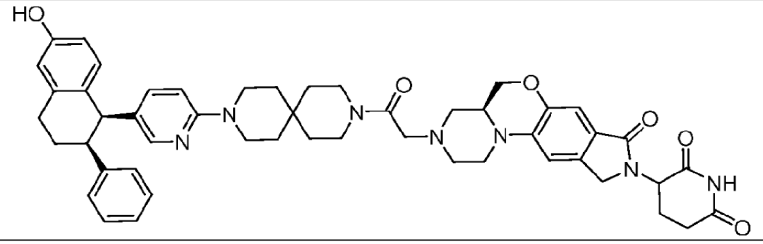
Compound No.	Chemical Structure	Chemical Name
B146		3-((S)-3-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B147		3-((S)-3-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B148*		3-((S)-3-(2-(9-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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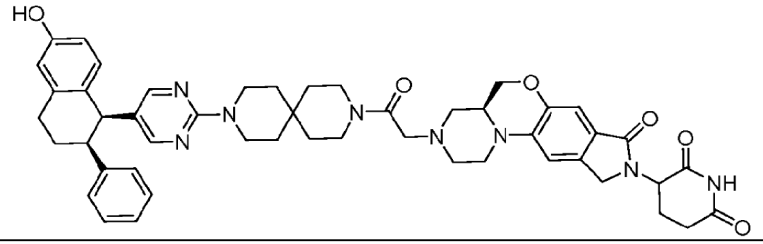
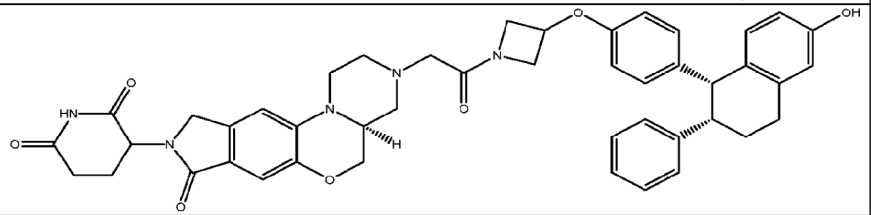
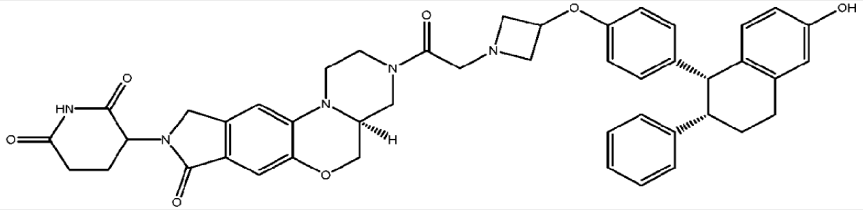
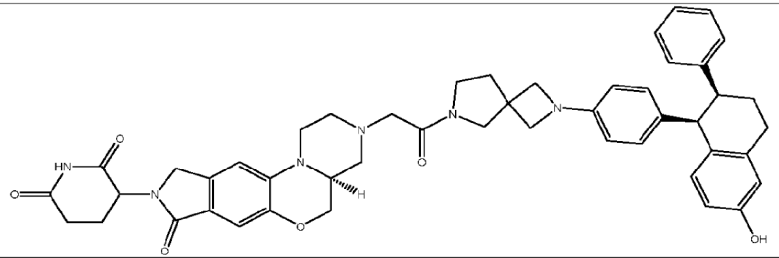
B149*		3-((S)-3-(2-(9-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B150		3-((S)-3-(2-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B151		3-((S)-3-(2-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B152		3-((S)-3-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.4]octan-6-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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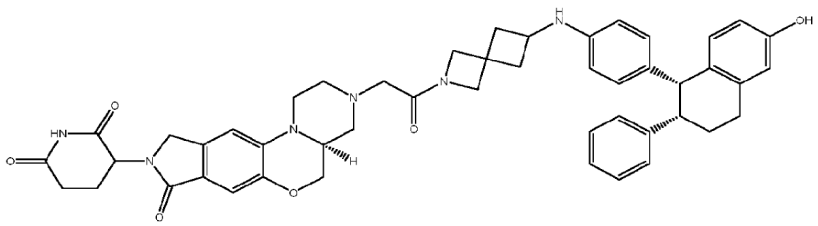
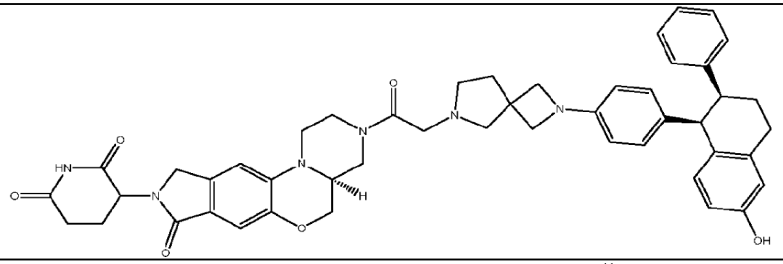
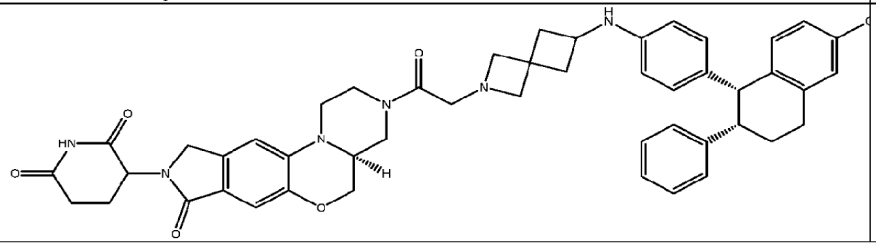
B153		3-((S)-3-(2-(6-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)-2-azaspiro[3.3]heptan-2-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B154		3-((S)-3-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.4]octan-6-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B155		3-((S)-3-(2-(6-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)-2-azaspiro[3.3]heptan-2-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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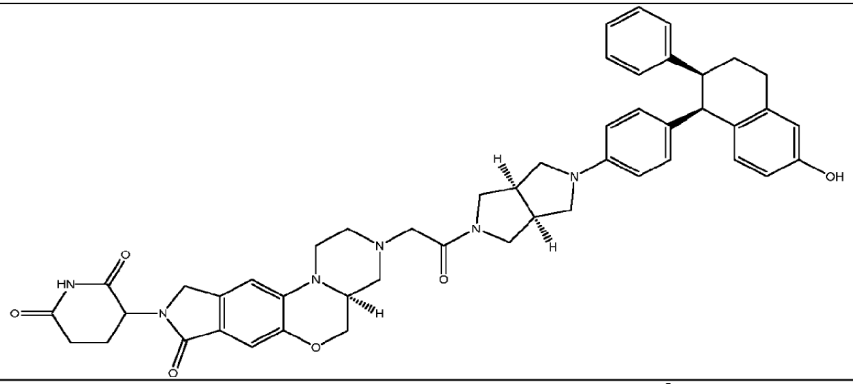
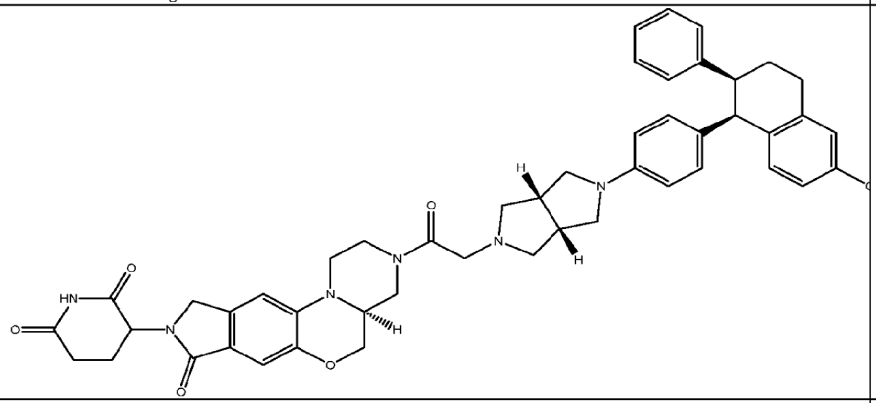
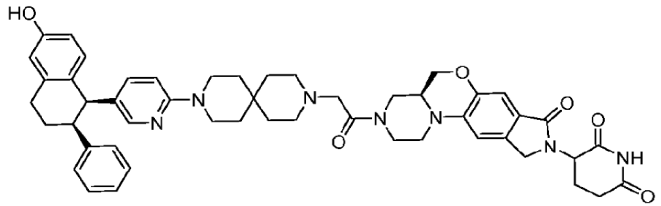
B156		3-((S)-3-(2-((3aR,6aS)-5-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-oxocthyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B157		3-((S)-3-(2-((3aR,6aS)-5-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B158*		3-((S)-3-(2-(9-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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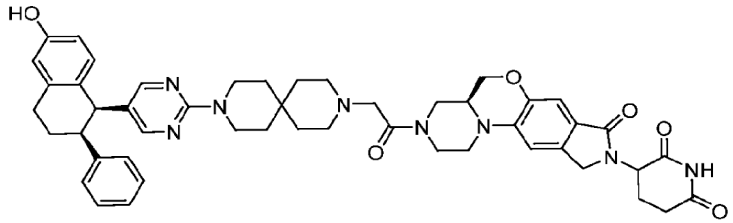
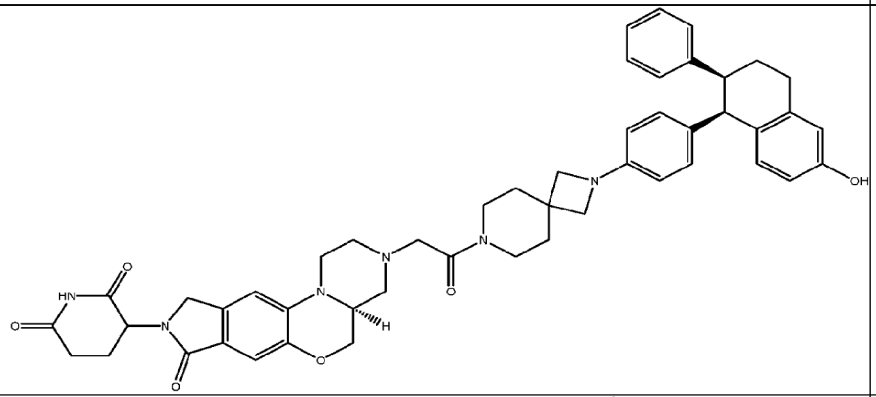
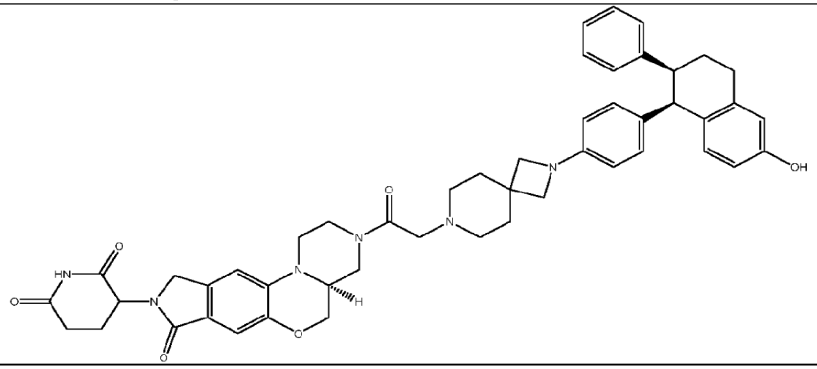
B159*		3-((S)-3-(2-(9-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B160		3-((S)-3-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B161		3-((S)-3-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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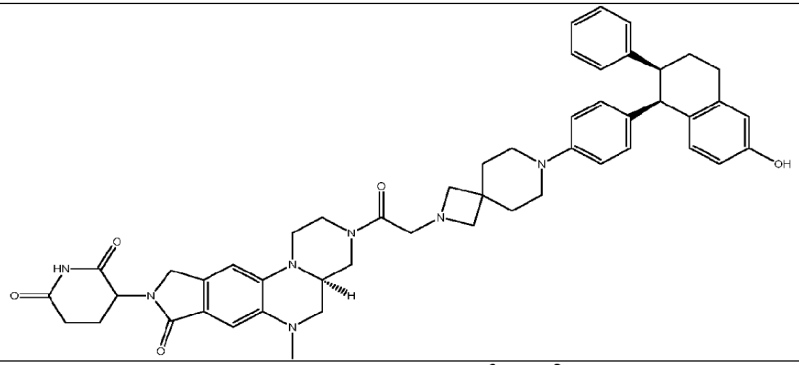
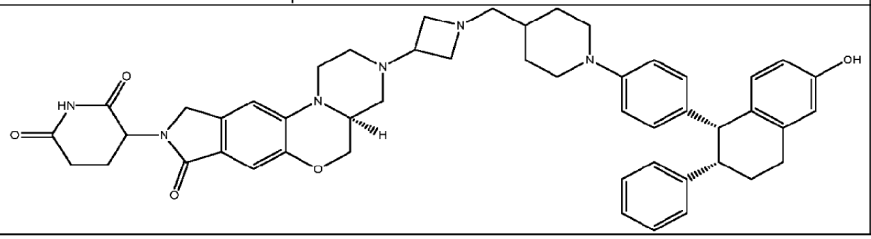
Compound No.	Chemical Structure	Chemical Name
B162		3-((R)-3-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-6-methyl-8-oxo-2,3,4,4a,5,6,8,10-octahydropyrazino[1,2-a]pyrrolo[3,4-g]quinoxalin-9(1H)-yl)piperidine-2,6-dione
B164		3-((S)-3-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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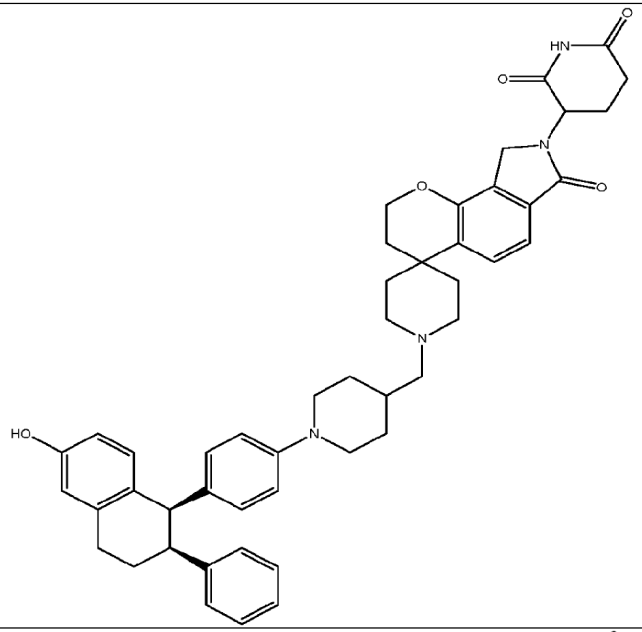
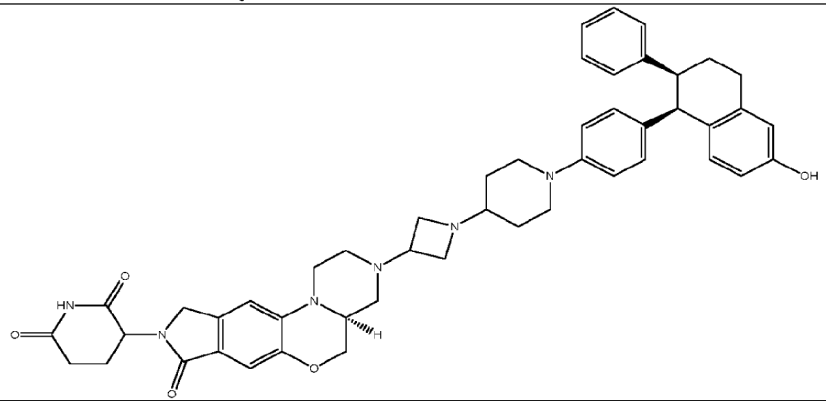
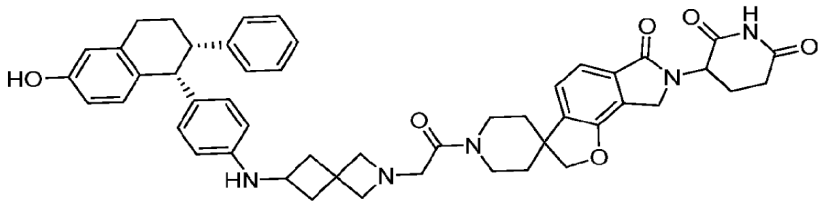
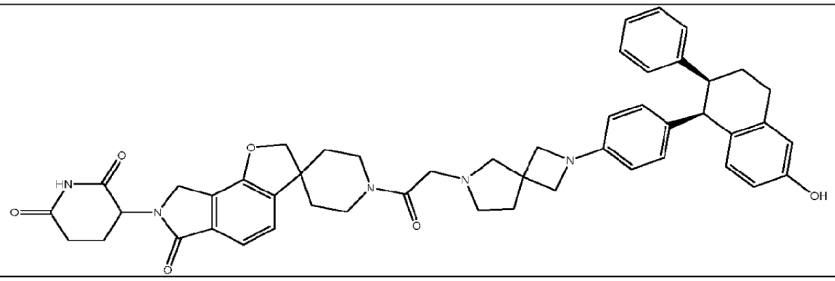
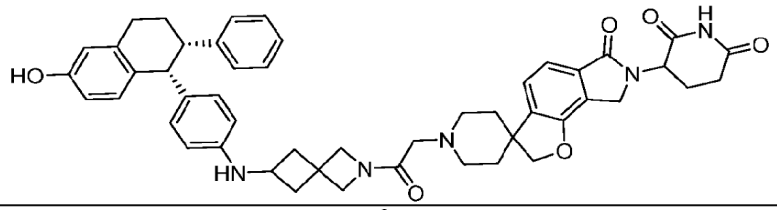
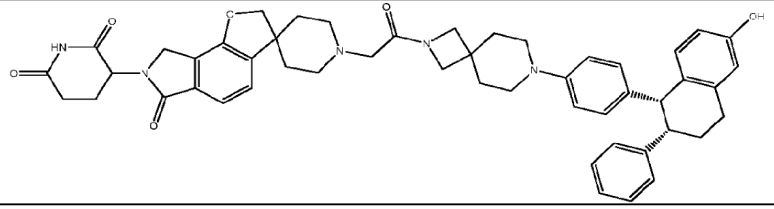
Compound No.	Chemical Structure	Chemical Name
B165		3-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-7'-oxo-2',3',7',9'-tetrahydro-8'H-spiro[piperidine-4,4'-pyrano[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
B167		3-((S)-3-(1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)azetidin-3-yl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B168		3-(1'-(2-(6-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)-2-azaspiro[3.3]heptan-2-yl)acetyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B169		3-(1'-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.4]octan-6-yl)acetyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B170		3-(1'-(2-(6-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)-2-azaspiro[3.3]heptan-2-yl)-2-oxocthyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B171		3-(1'-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

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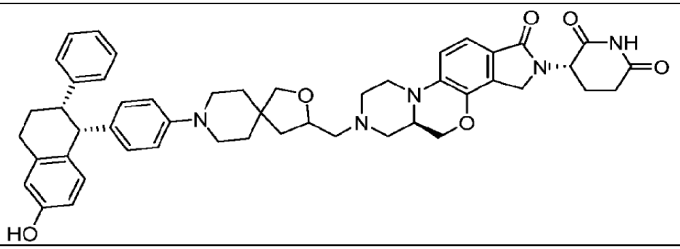
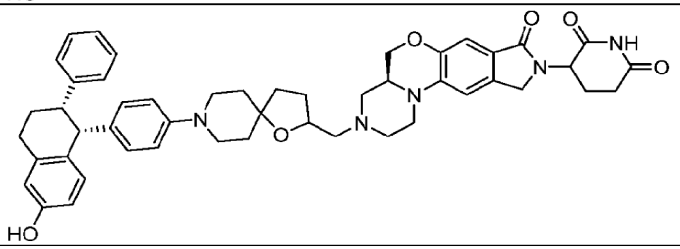
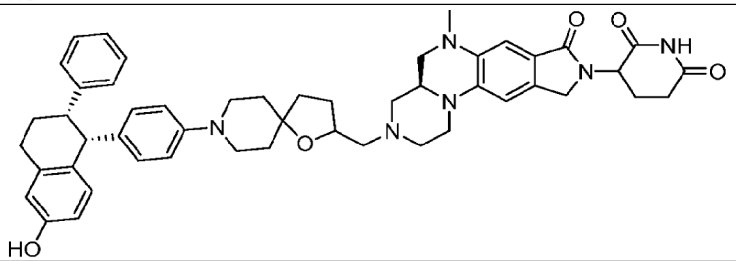
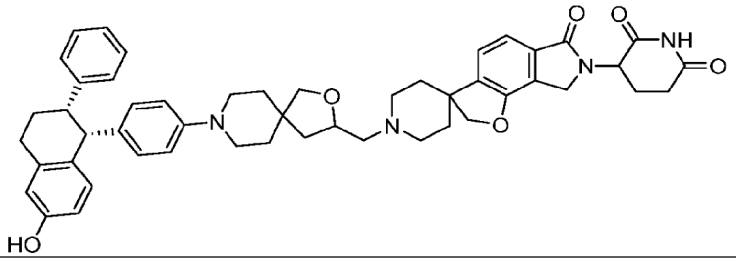
B172		(3S)-3-((5aR)-7-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B173		3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B174		3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-methyl-8-oxo-2,3,4,4a,5,6,8,10-octahydropyrazino[1,2-a]pyrrolo[3,4-g]quinoxalin-9(1H)-yl)piperidine-2,6-dione
B175		3-(1'-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

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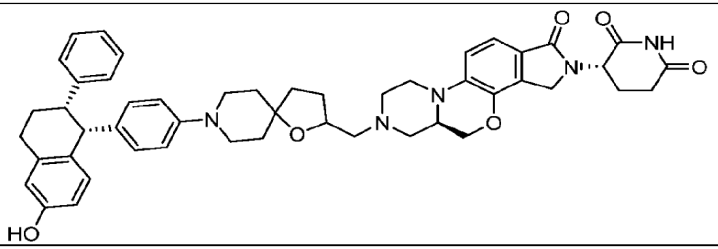
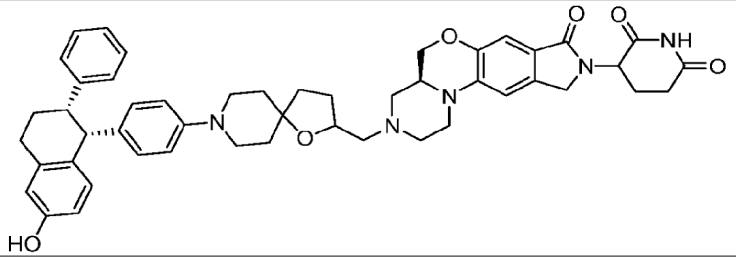
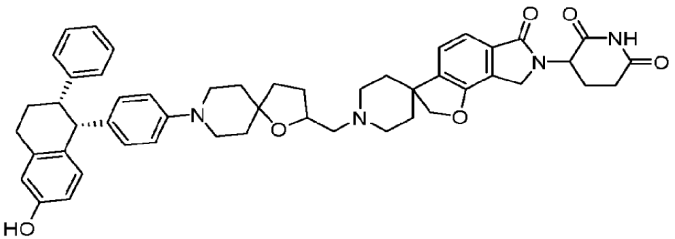
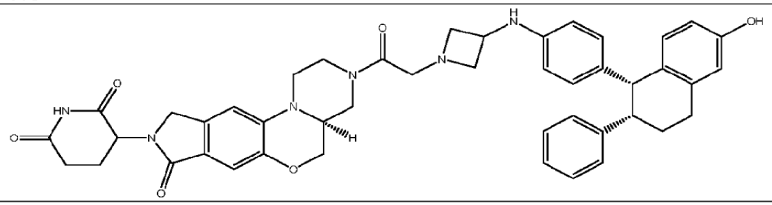
B176		(3S)-3-((5aR)-7-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B177		3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B178		3-(1'-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B204		3-((S)-3-(2-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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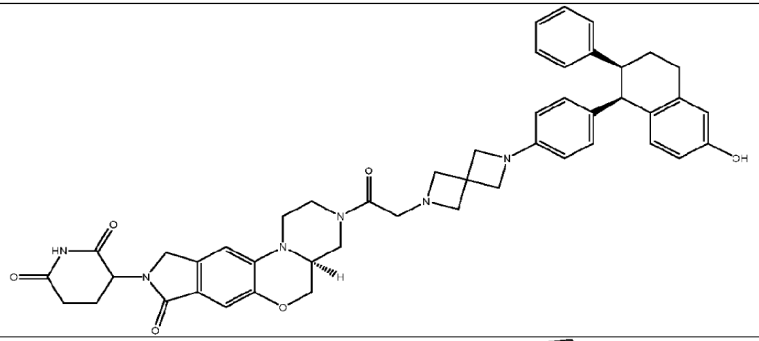
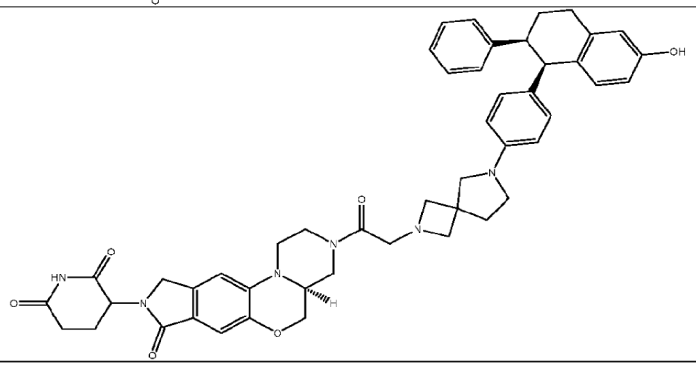
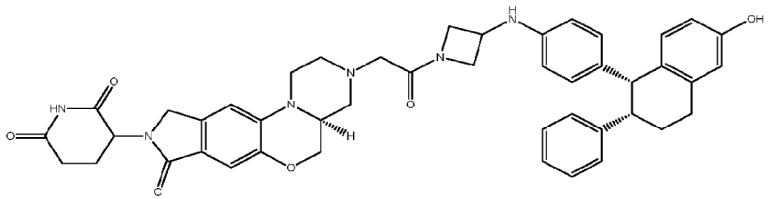
B205		3-((S)-3-(2-(6-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.3]heptan-2-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B206		3-((S)-3-(2-(6-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.4]octan-2-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B207		3-((S)-3-(2-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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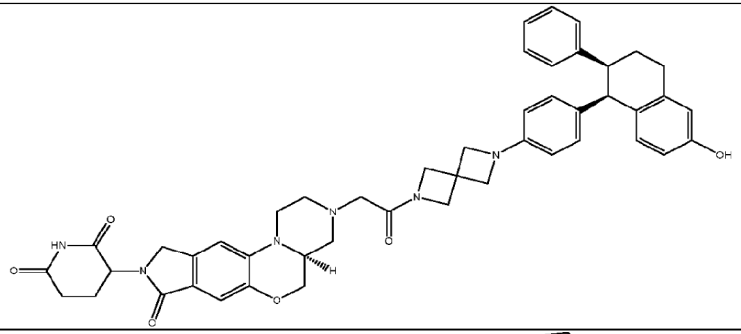
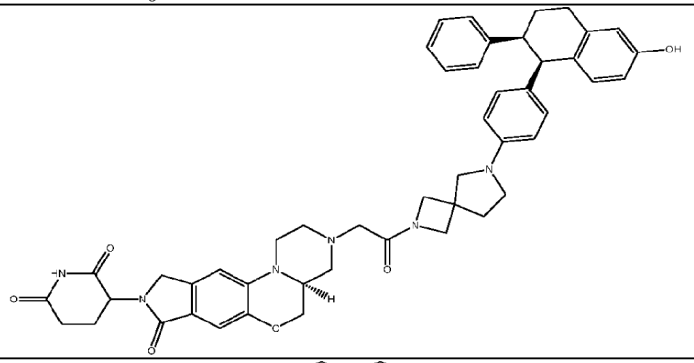
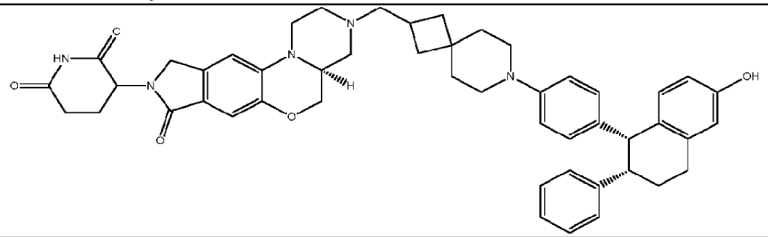
B208		3-((S)-3-(2-(6-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.3]heptan-2-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B209		3-((S)-3-(2-(6-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.4]octan-2-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B211		3-((S)-3-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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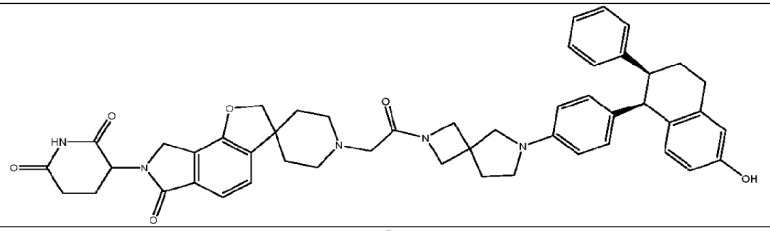
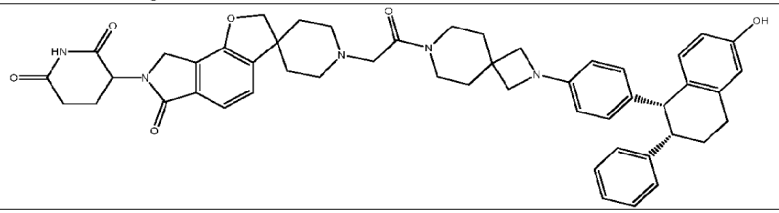
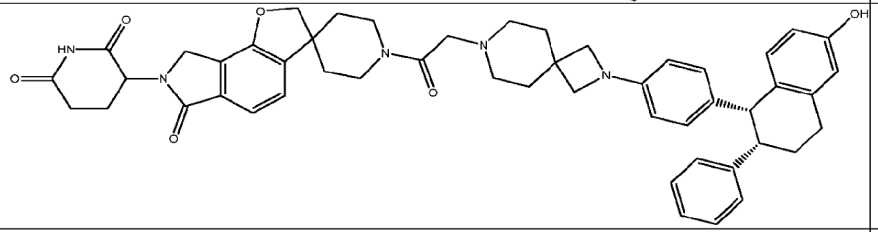
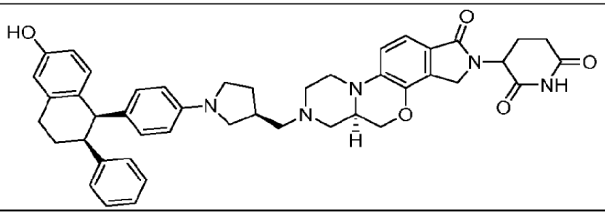
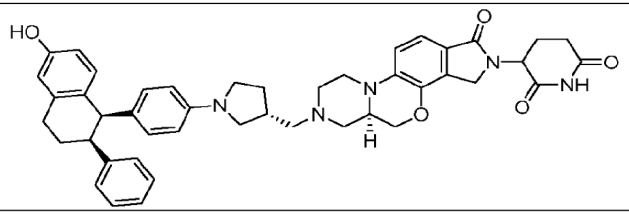
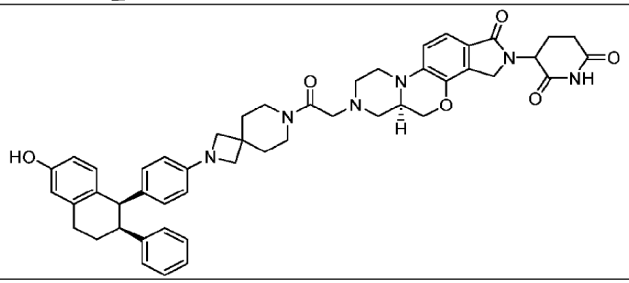
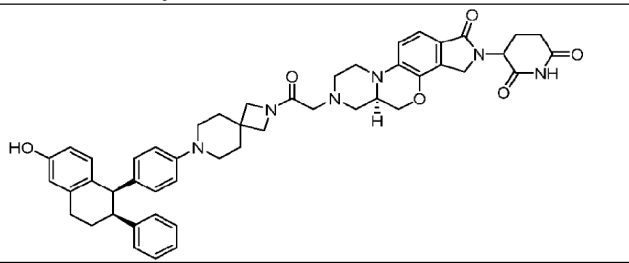
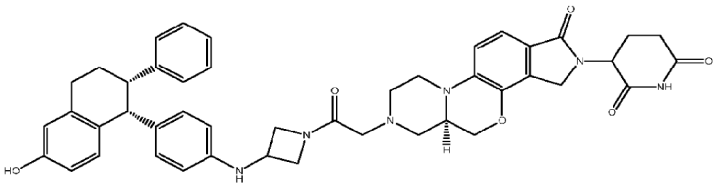
B212		3-(1'-(2-(6-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.4]octan-2-yl)-2-oxoethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B213		3-(1'-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)-2-oxoethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B214		3-(1'-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B215		3-((R)-7-(((S)-1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)pyrrolidin-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B216		3-((R)-7-(((R)-1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)pyrrolidin-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B218		3-((R)-7-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)-2-oxoethyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B219		3-((R)-7-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B220		3-((R)-7-(2-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)-2-oxoethyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

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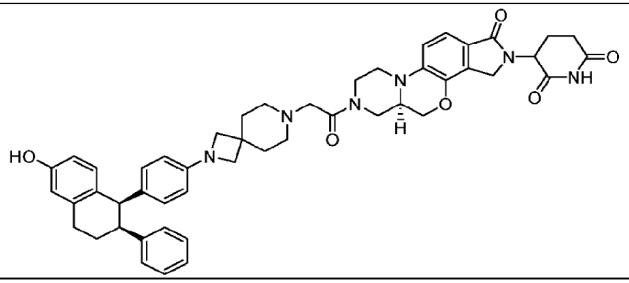
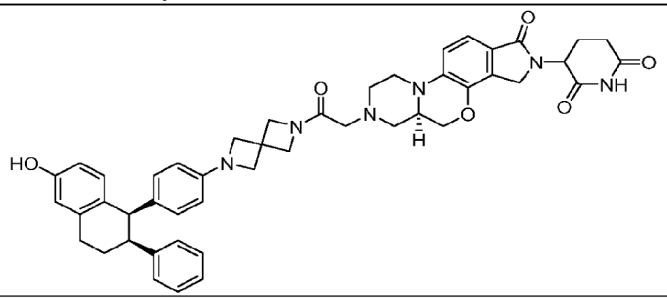
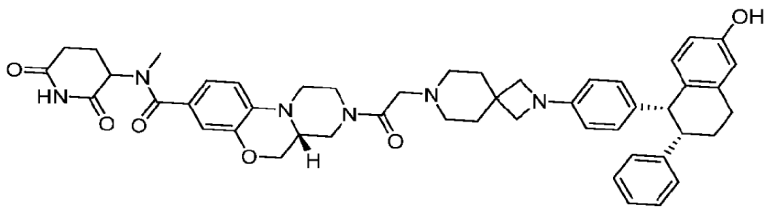
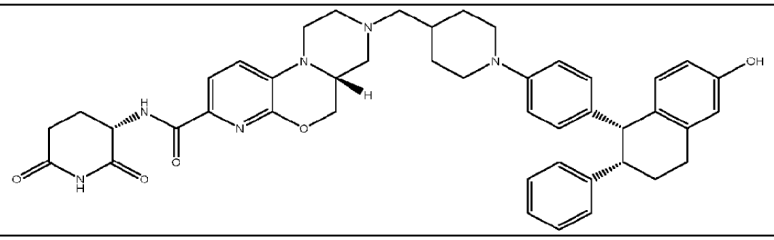
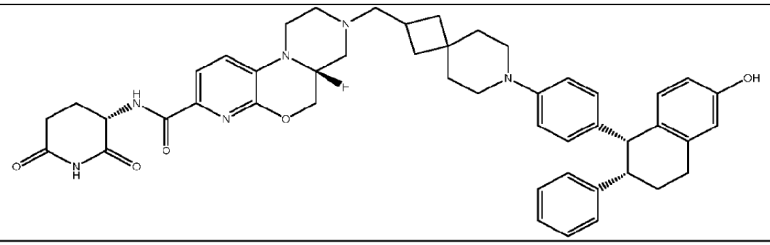
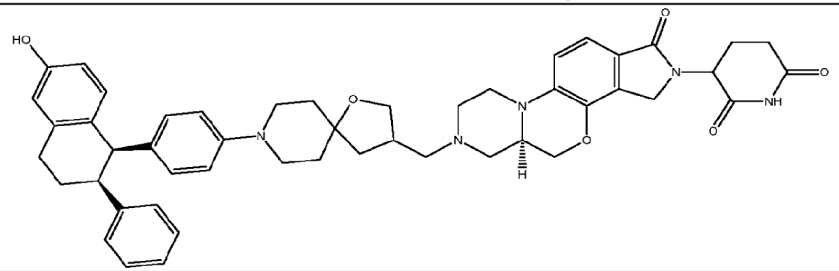
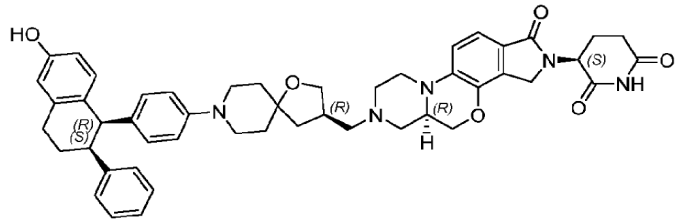
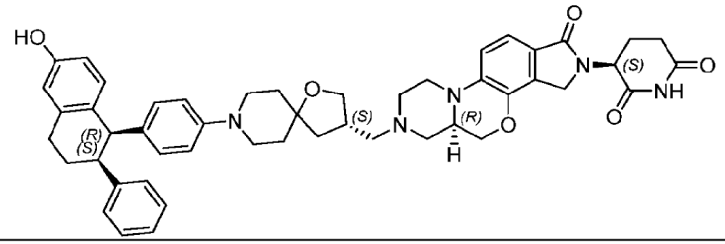
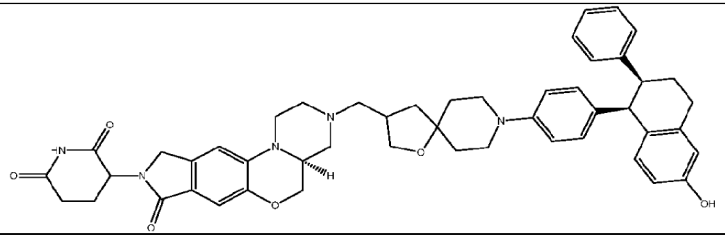
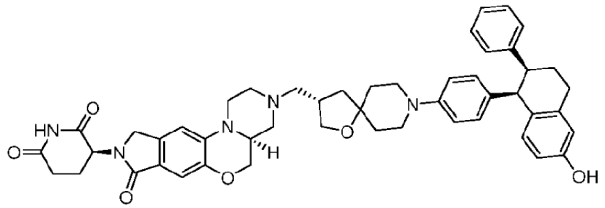
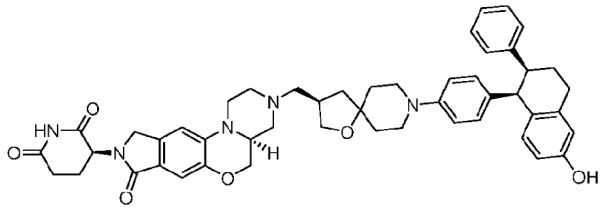
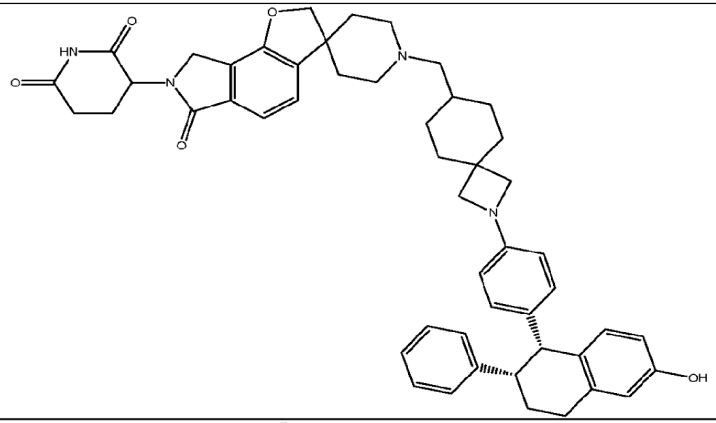
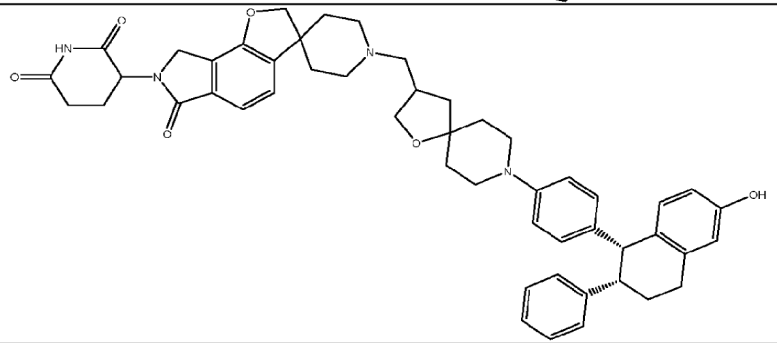
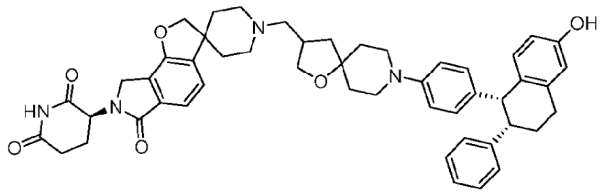
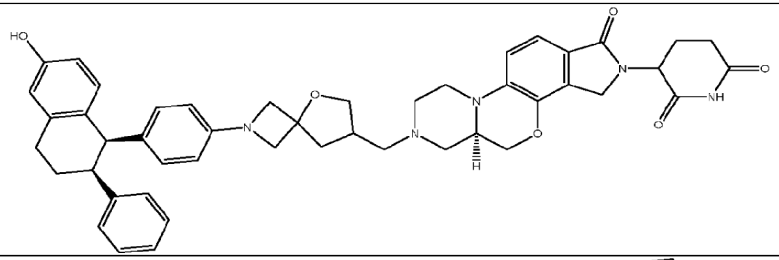
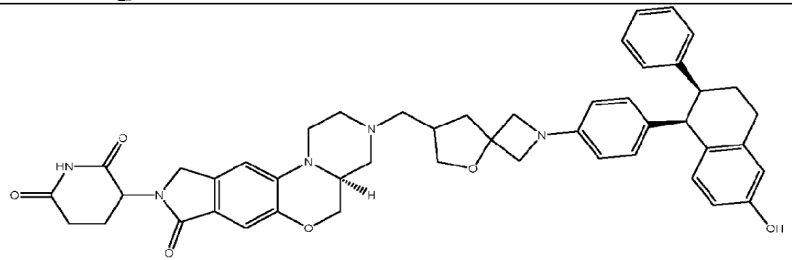
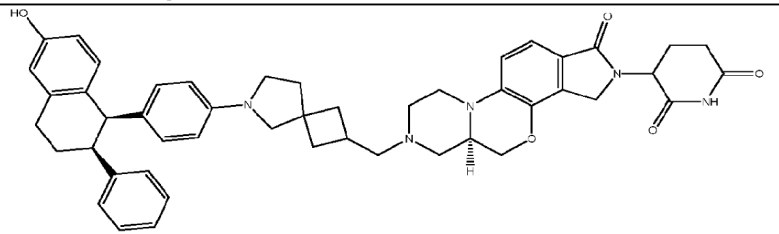
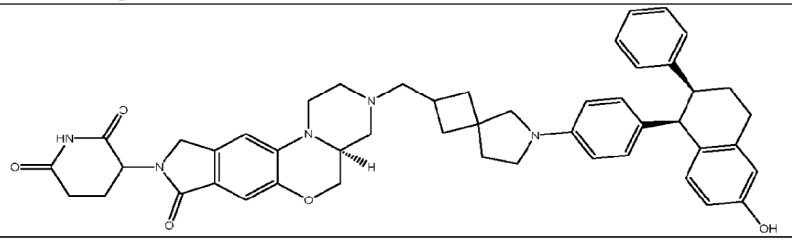
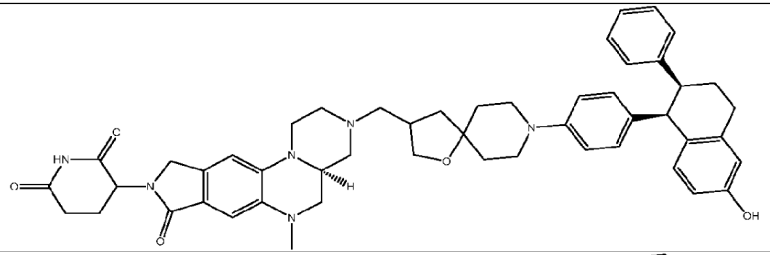
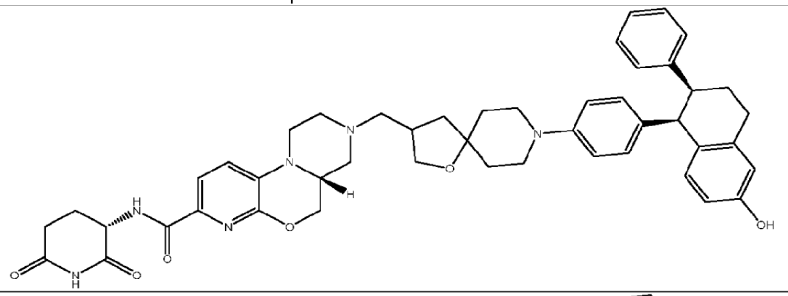
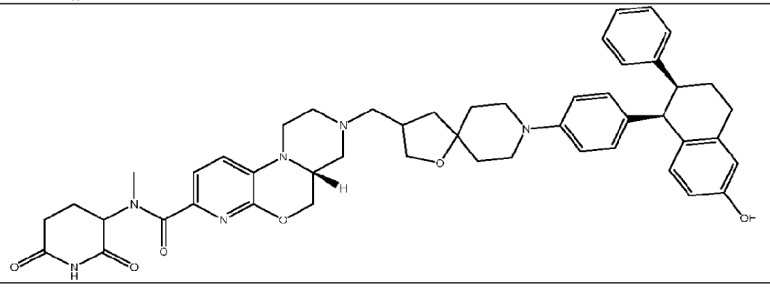
Compound No.	Chemical Structure	Chemical Name
B221		3-((R)-7-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B222		3-((R)-7-(2-(6-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.3]heptan-2-yl)-2-oxoethyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B223		(4aR)-N-(2,6-dioxopiperidin-3-yl)-3-(2-(2-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-N-methyl-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxamide
B224		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide

Compound No.	Chemical Structure	Chemical Name
B225		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
B226		3-((5aR)-7-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B226X		(S)-3-((R)-7-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B226Y		(S)-3-((R)-7-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B227		3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B227X		(S)-3-((S)-3-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B227Y		(S)-3-((S)-3-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B228		3-(1'-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B229		3-(1'-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B229X		(3S)-3-(1'-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B230		3-((5aR)-7-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B231		3-((4aS)-3-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B232		3-((R)-7-((6-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-6-azaspiro[3.4]octan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B233		3-((S)-3-((6-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-6-azaspiro[3.4]octan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B234		3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-methyl-8-oxo-2,3,4,4a,5,6,8,10-octahydropyrazino[1,2-a]pyrrolo[3,4-g]quinoxalin-9(1H)-yl)piperidine-2,6-dione
B236		(4aR)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
B237		(4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-N-methyl-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide

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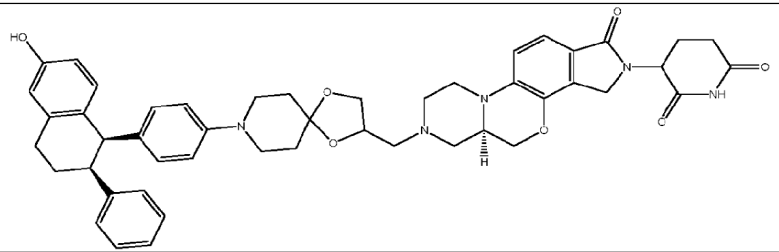
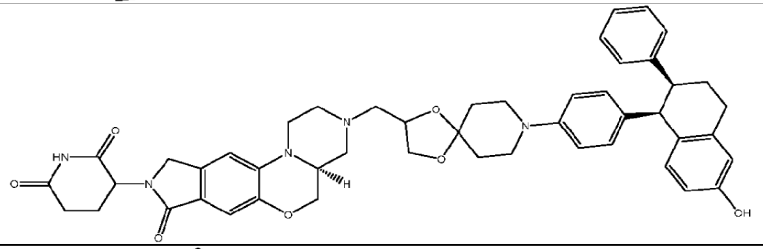
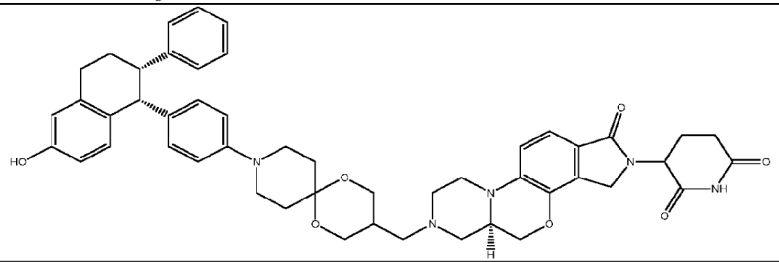
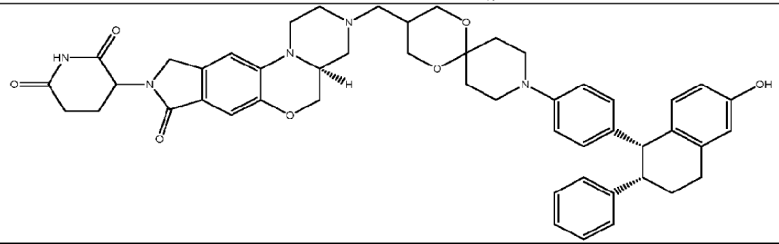
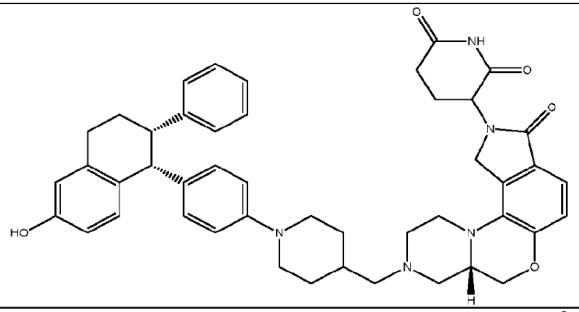
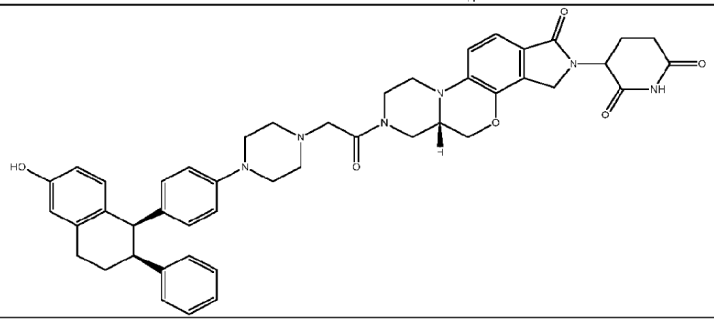
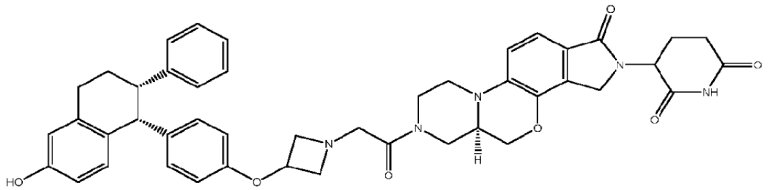
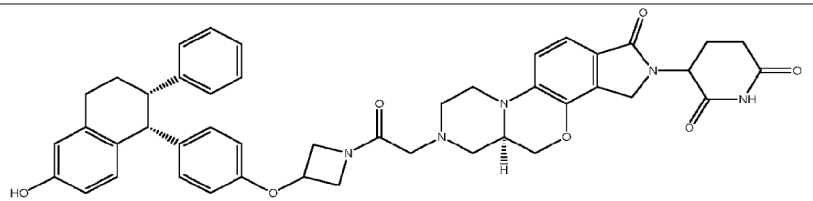
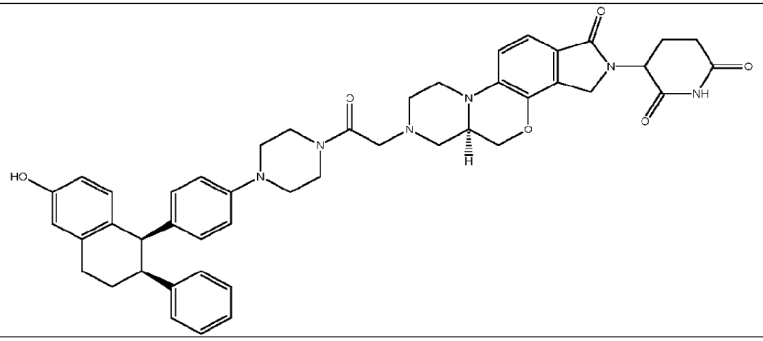
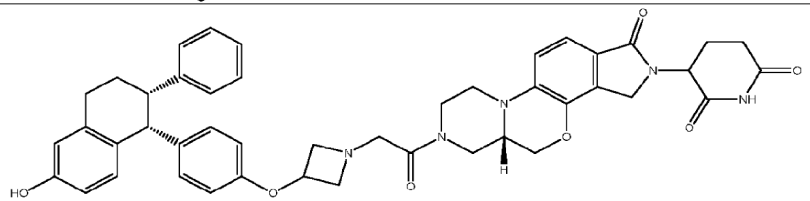
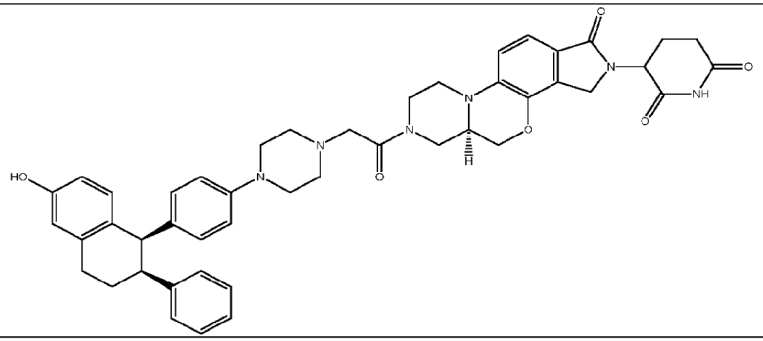
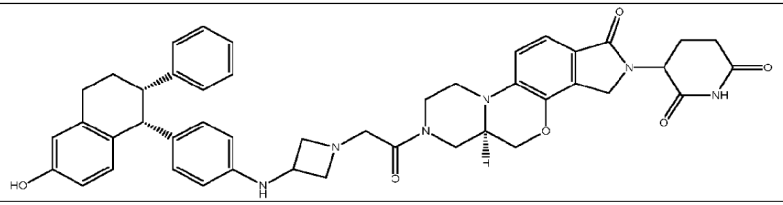
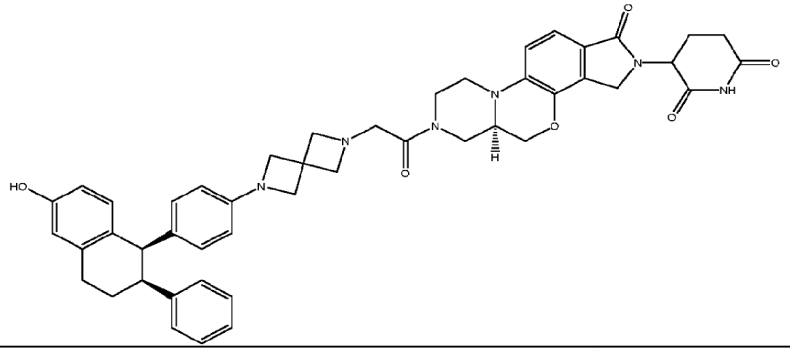
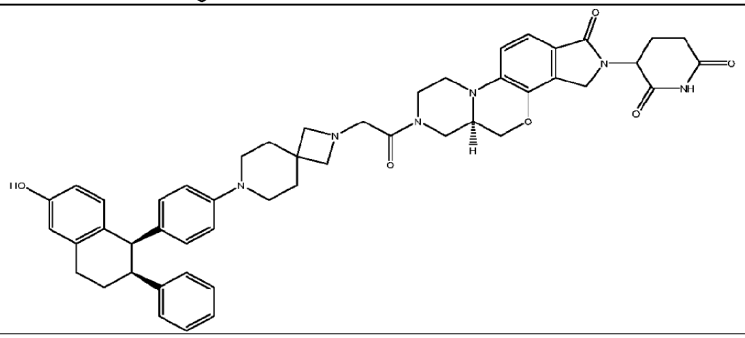
Compound No.	Chemical Structure	Chemical Name
B238		3-((5aR)-7-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,4-dioxa-8-azaspiro[4.5]decan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B239		3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,4-dioxa-8-azaspiro[4.5]decan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B240		3-((R)-7-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B242		3-((S)-3-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B243		3-((S)-9-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-3-oxo-1,3,7,7a,8,9,10,11-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[3,2-e]isoindol-2-yl)piperidine-2,6-dione
B244		3-((S)-7-(2-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)acetyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B245		3-((R)-7-(2-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)acetyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B246		3-((R)-7-(2-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)-2-oxoethyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B247		3-((R)-7-(2-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)-2-oxoethyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B248		3-((S)-7-(2-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)acetyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B249		3-((R)-7-(2-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)acetyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B250		3-((R)-7-(2-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)acetyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B251		3-((R)-7-(2-(6-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.3]heptan-2-yl)acetyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B252		3-((R)-7-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

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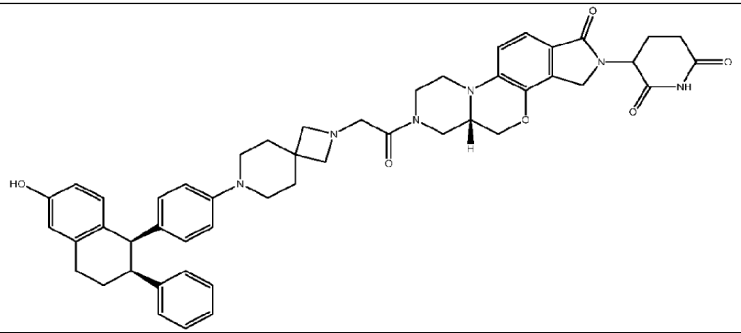
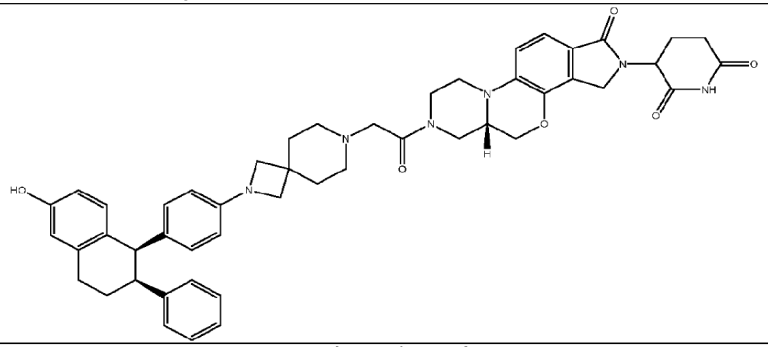
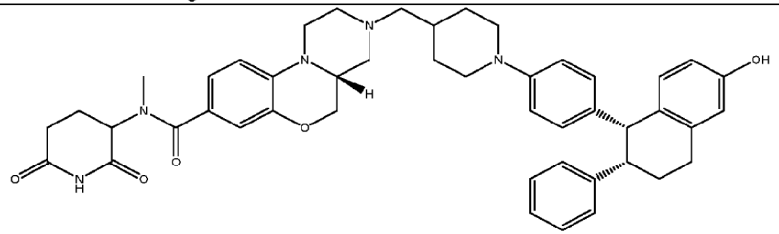
Compound No.	Chemical Structure	Chemical Name
B253		3-((S)-7-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B254		3-((S)-7-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B255		(4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-N-methyl-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxamide

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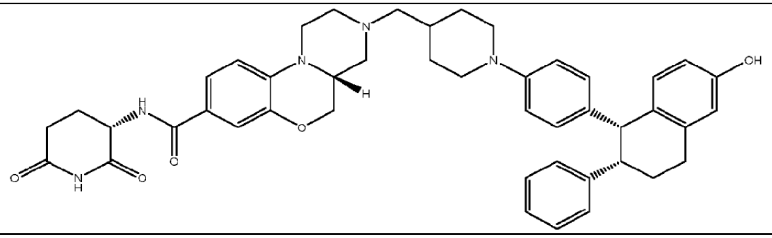
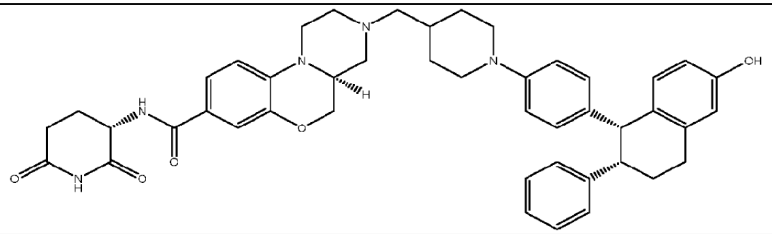
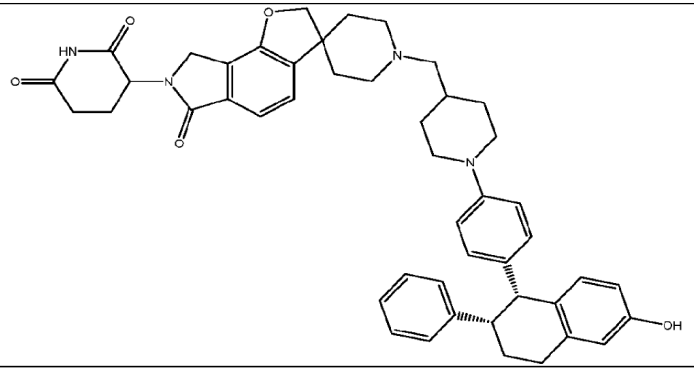
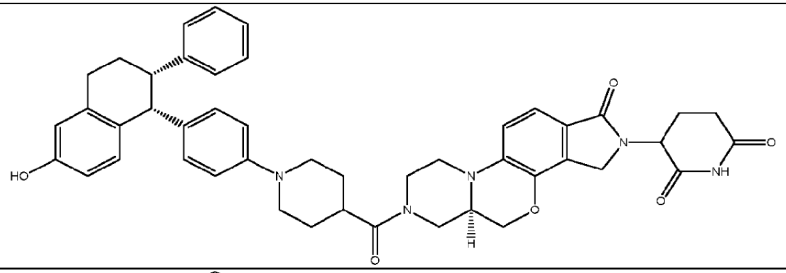
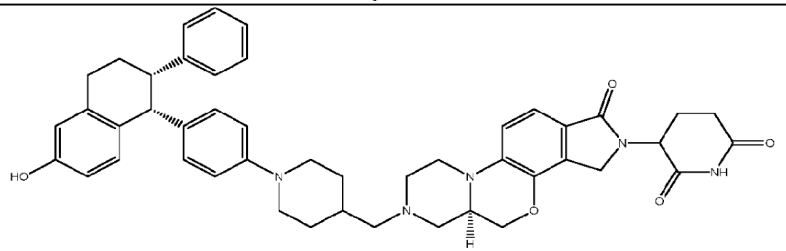
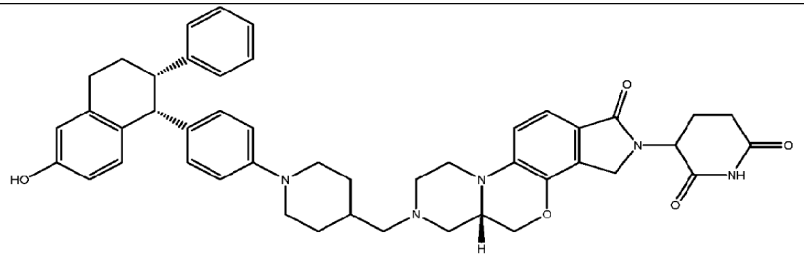
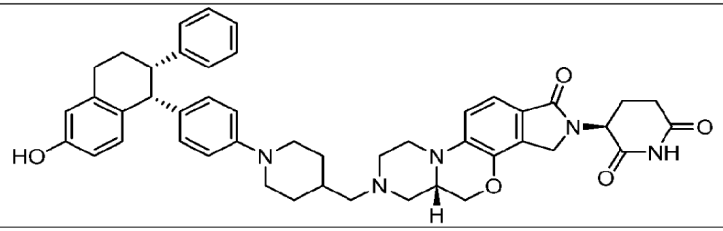
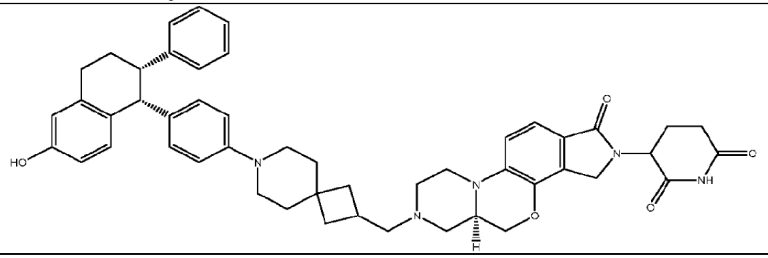
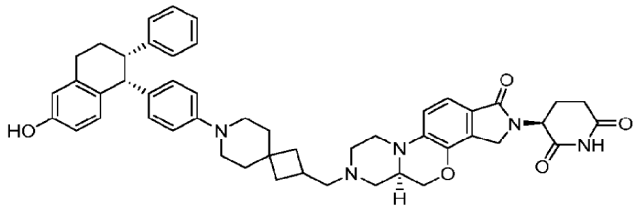
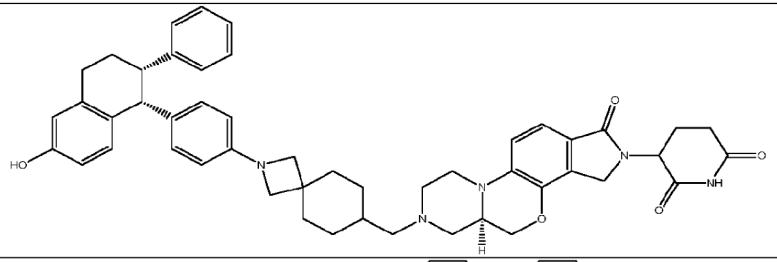
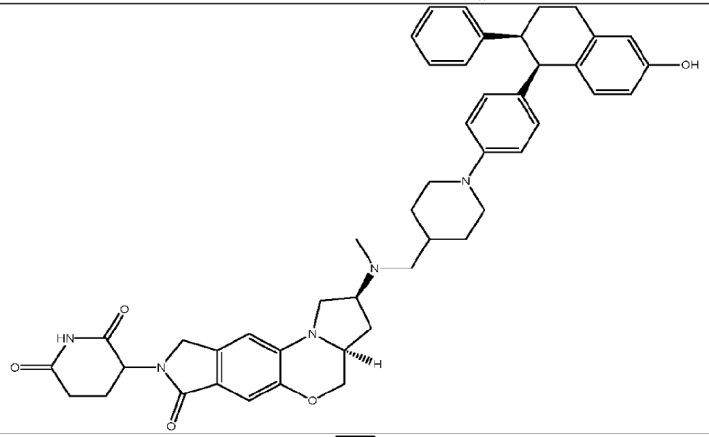
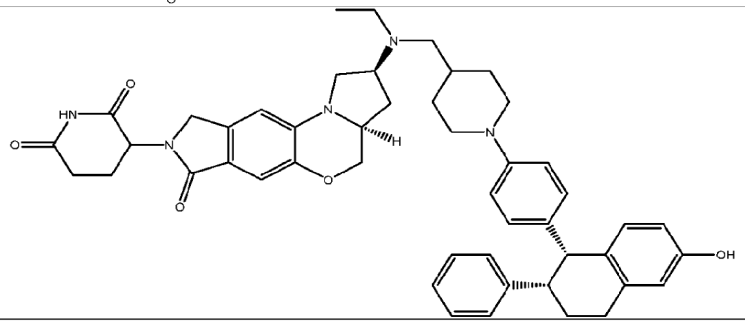
Compound No.	Chemical Structure	Chemical Name
B256		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxamide
B257		(S)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxamide
B258		3-(1'-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B295		3-((R)-7-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine-4-carbonyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B298		3-((R)-7-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B306		3-((S)-7-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B306X		(S)-3-((S)-7-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B307		3-((2S,3aS)-2-(((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)amino)-7-oxo-2,3,3a,4,7,9-hexahydro-1H,8H-pyrrolo[1',2':4,5][1,4]oxazino[2,3-f]isoindol-8-yl)piperidine-2,6-dione
B308		3-((R)-7-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B308X		(S)-3-((R)-7-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B309		3-((R)-7-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-c]isoindol-2-yl)piperidine-2,6-dione
B310		3-((2S,3aS)-2-(((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)(methyl)amino)-7-oxo-2,3,3a,4,7,9-hexahydro-1H,8H-pyrrolo[1',2':4,5][1,4]oxazino[2,3-f]isoindol-8-yl)piperidine-2,6-dione
B311		3-((2S,3aS)-2-(ethyl((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)amino)-7-oxo-2,3,3a,4,7,9-hexahydro-1H,8H-pyrrolo[1',2':4,5][1,4]oxazino[2,3-f]isoindol-8-yl)piperidine-2,6-dione

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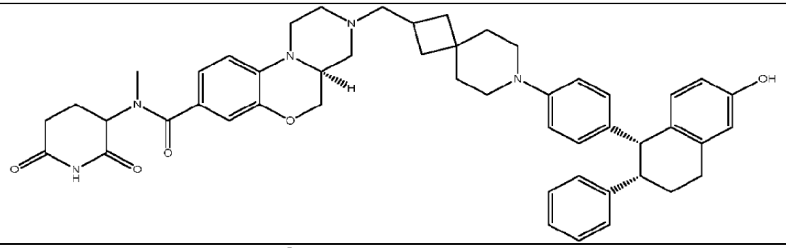
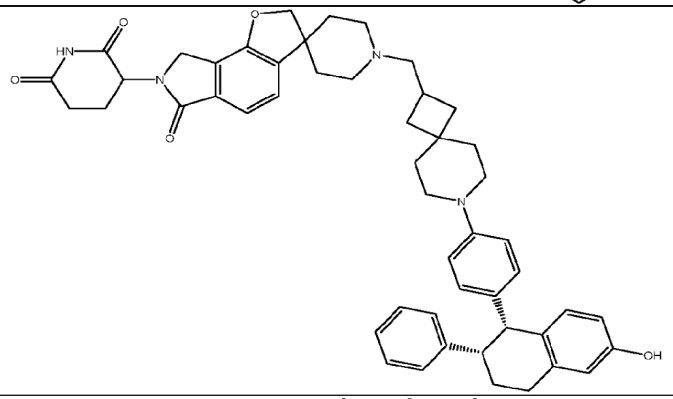
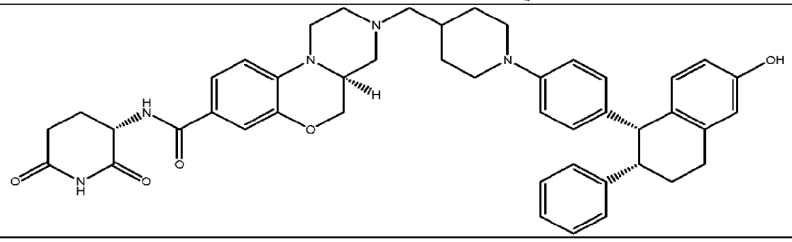
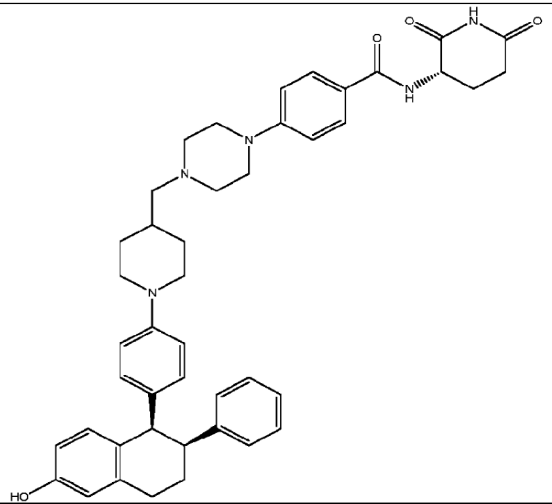
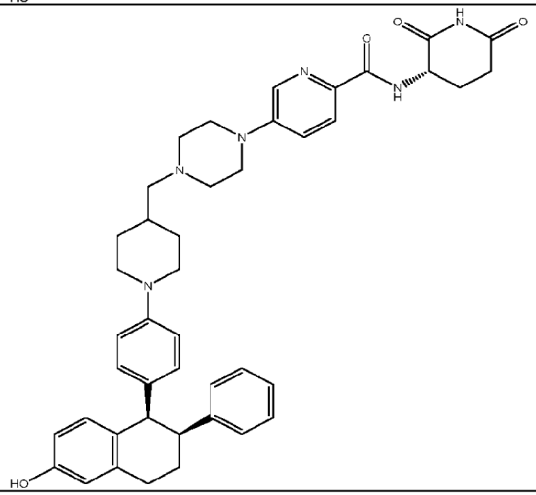
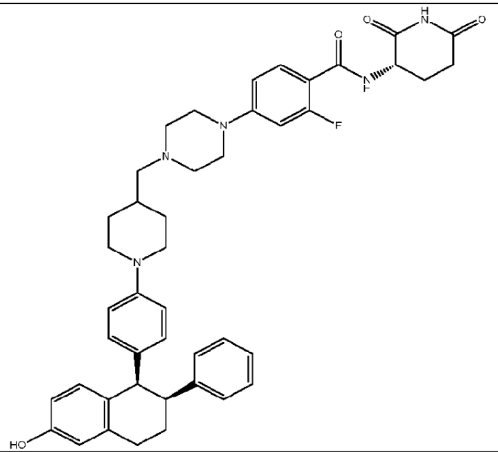
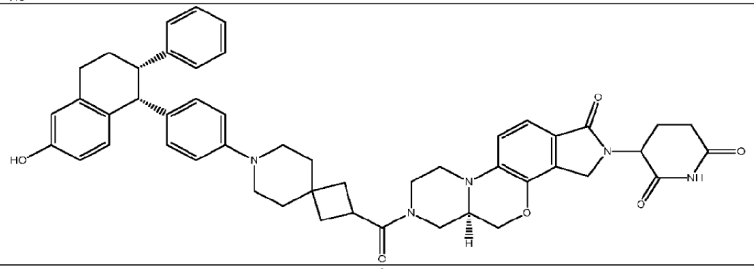
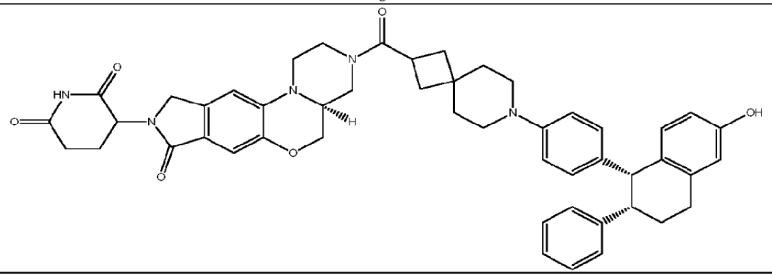
Compound No.	Chemical Structure	Chemical Name
B312		(4aS)-N-(2,6-dioxopiperidin-3-yl)-3-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-N-methyl-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxamide
B313		3-(1'-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B314		(S)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxamide

Compound No.	Chemical Structure	Chemical Name
B315		N-((S)-2,6-dioxopiperidin-3-yl)-4-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)benzamide
B316		N-((S)-2,6-dioxopiperidin-3-yl)-5-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide

Compound No.	Chemical Structure	Chemical Name
B317		N-((S)-2,6-dioxopiperidin-3-yl)-2-fluoro-4-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)benzamide
B318		3-((R)-7-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbonyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B319		3-((S)-3-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbonyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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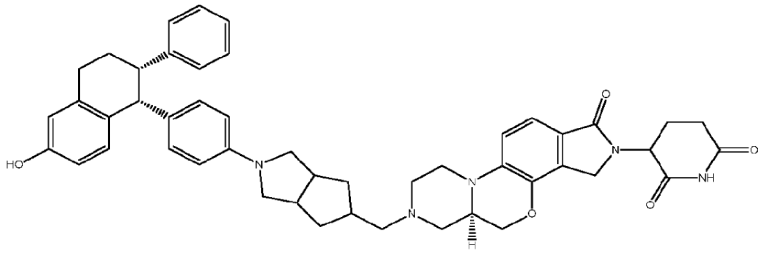
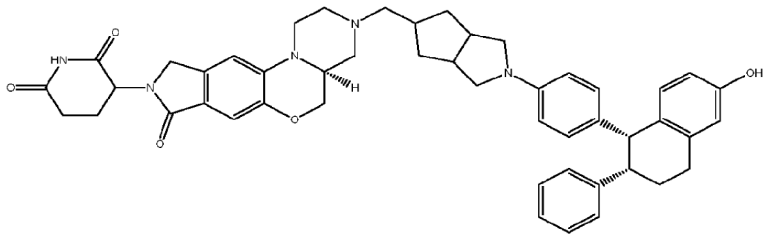
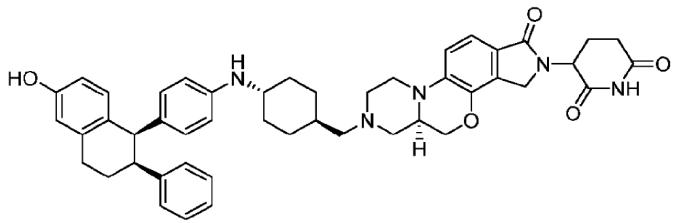
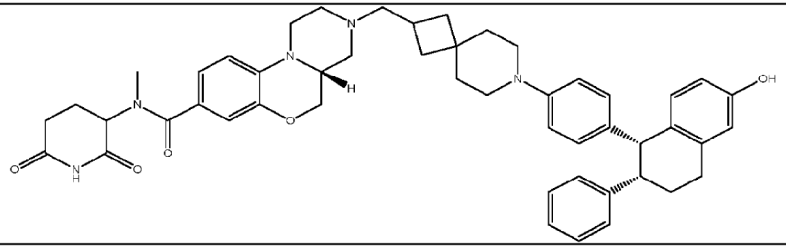
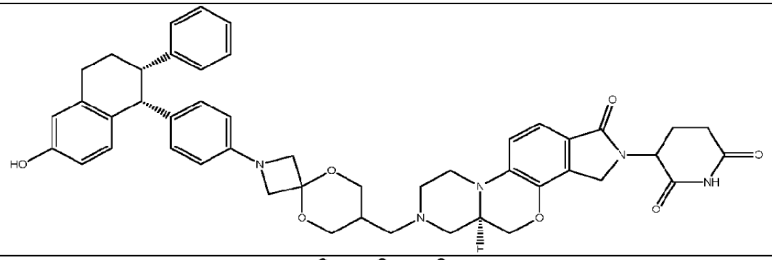
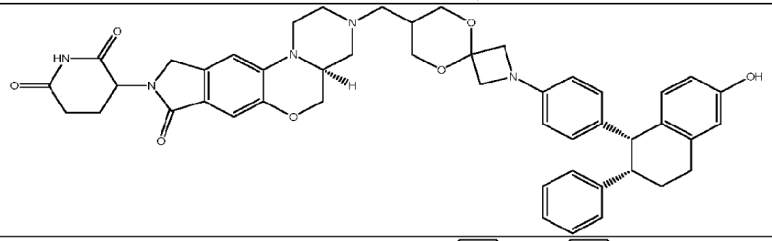
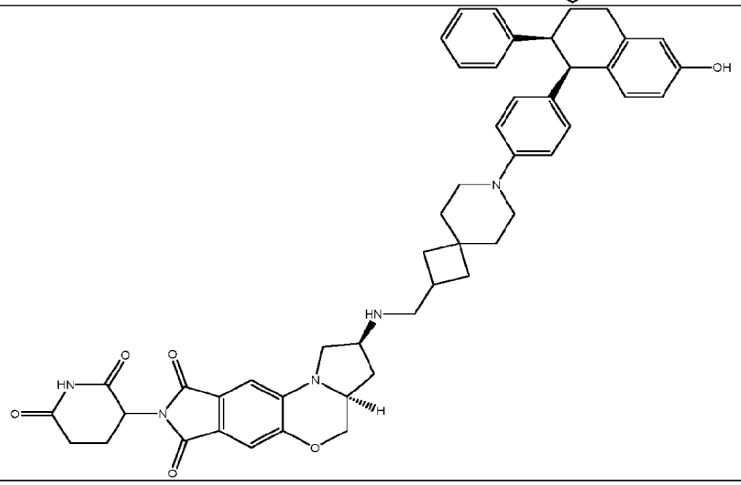
Compound No.	Chemical Structure	Chemical Name
B320		3-((5aR)-7-(((3aRS,6aSR)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)octahydrocyclopenta[c]pyrrol-5-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-c]isoindol-2-yl)piperidine-2,6-dione
B321		3-((4aS)-3-(((3aRS,6aSR)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)octahydrocyclopenta[c]pyrrol-5-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B322		3-((R)-7-(((1R,4R)-4-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)cyclohexyl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B326		(4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-N-methyl-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxamide

Compound No.	Chemical Structure	Chemical Name
B327		3-((R)-7-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5,9-dioxa-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B328		3-((S)-3-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5,9-dioxa-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B329		(2S,3aS)-8-(2,6-dioxopiperidin-3-yl)-2-(((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)amino)-2,3,3a,4-tetrahydro-1H,7H-pyrrolo[1',2':4,5][1,4]oxazino[2,3-f]isoindole-7,9(8H)-dione

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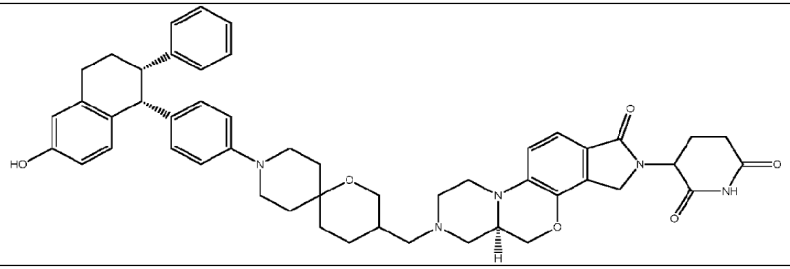
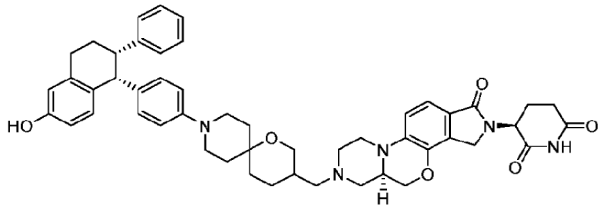
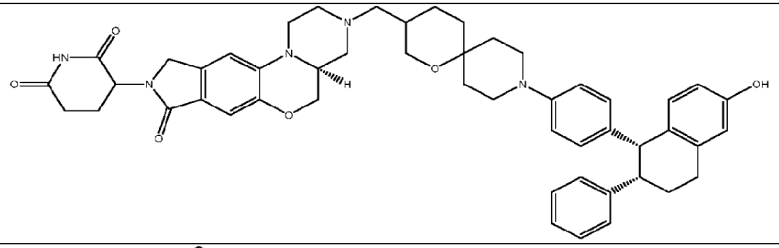
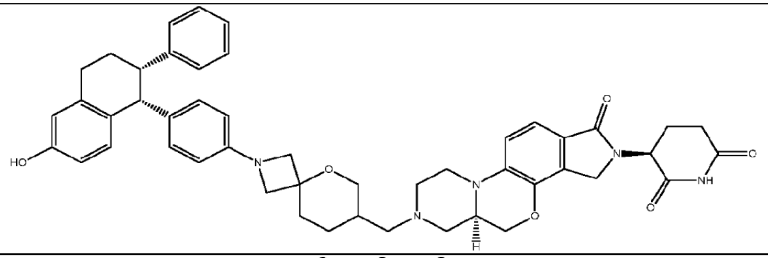
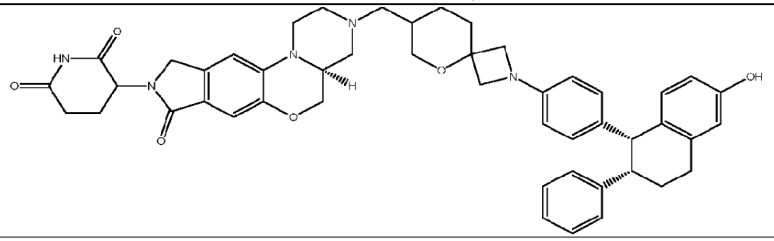
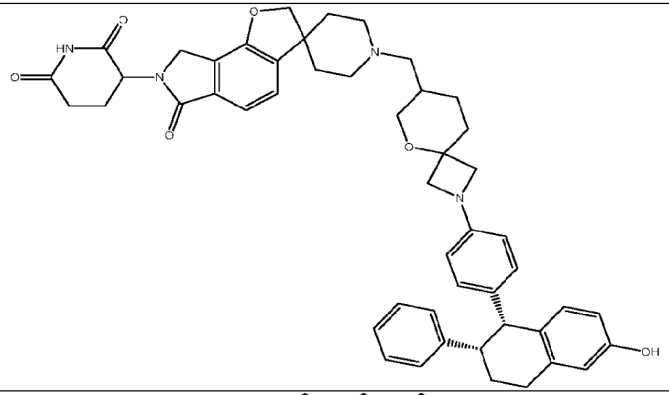
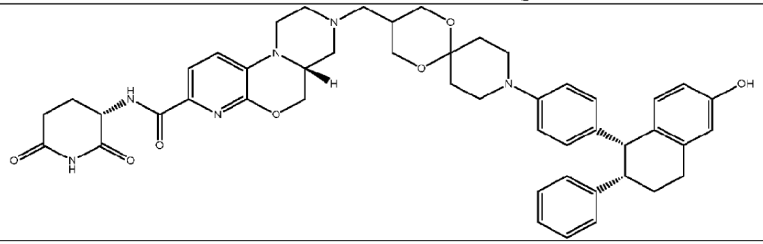
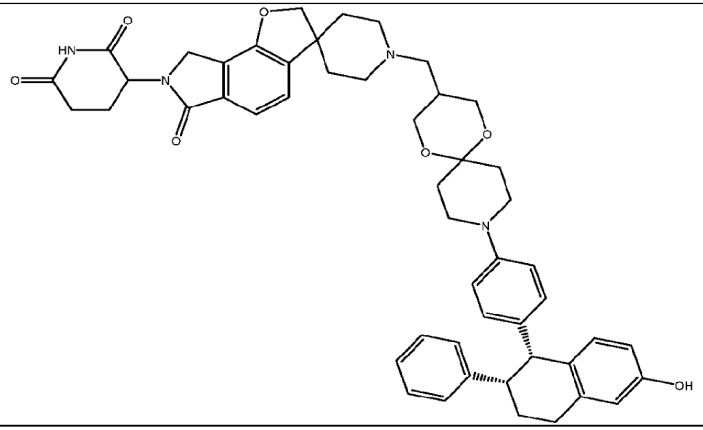
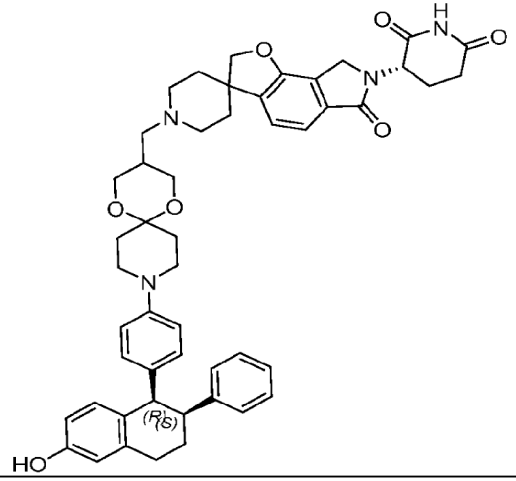
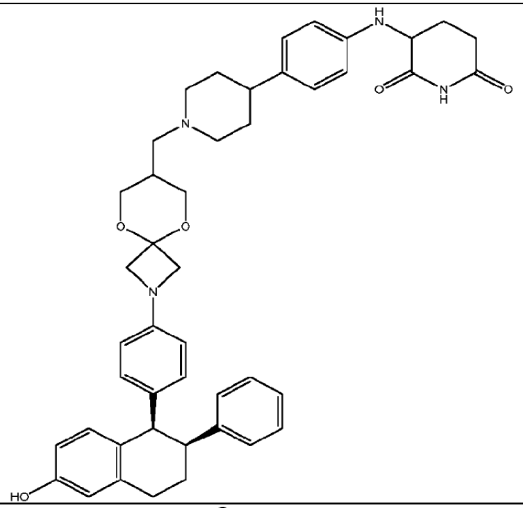
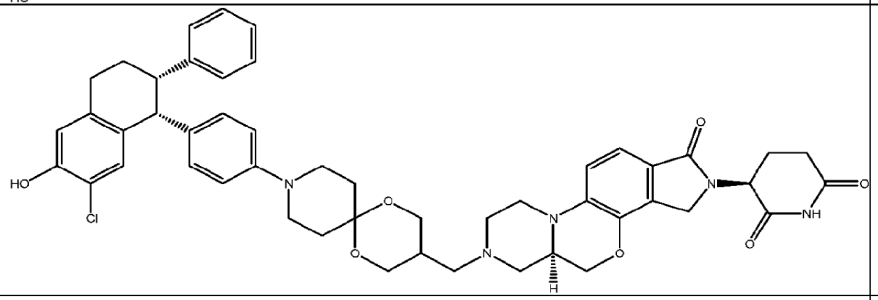
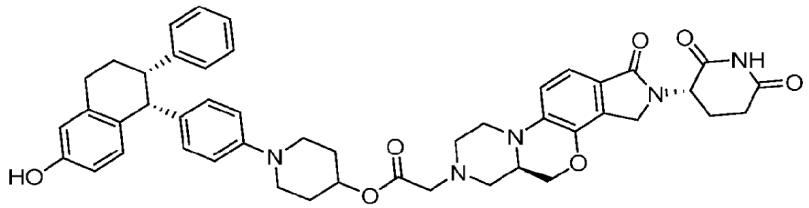
Compound No.	Chemical Structure	Chemical Name
B330		3-((5aR)-7-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B330X		(3S)-3-((5aR)-7-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B331		(2S,3aS)-8-(2,6-dioxopiperidin-3-yl)-2-(((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)(methyl)amino)-2,3,3a,4-tetrahydro-1H,7H-pyrrolo[1',2':4,5][1,4]oxazino[2,3-f]isoindole-7,9(8H)-dione

Compound No.	Chemical Structure	Chemical Name
B332		3-((4aS)-3-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B333		(3S)-3-((5aR)-7-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B334		3-((4aS)-3-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B335		3-(1'-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B336		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide

Compound No.	Chemical Structure	Chemical Name
B337		3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B337X		(S)-3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B339		3-((4-(1-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5,9-dioxa-2-azaspiro[3.5]nonan-7-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
B340		(S)-3-((R)-7-((9-(4-((1R,2S)-7-chloro-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B341		1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl 2-((R)-2-((S)-2,6-dioxopiperidin-3-yl)-1-oxo-2,3,5a,6,8,9-hexahydro-1H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-7(5H)-yl)acetate

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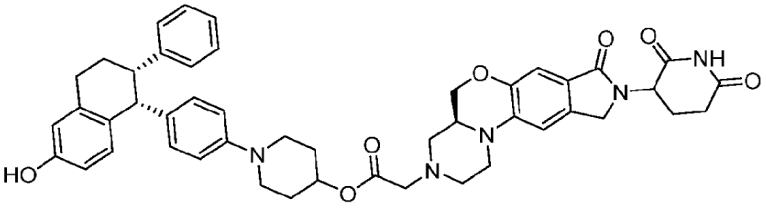
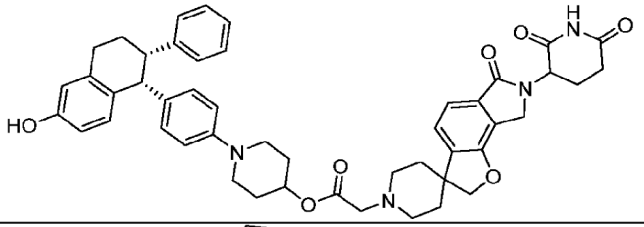
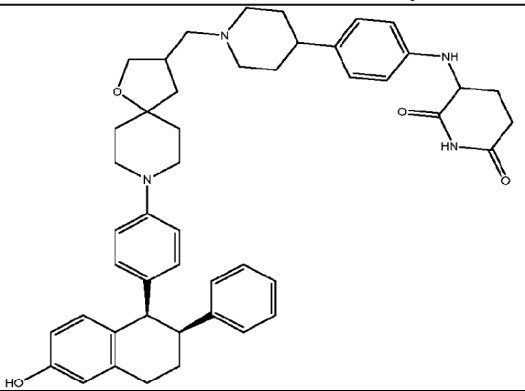
Compound No.	Chemical Structure	Chemical Name
B342		1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl 2-((4aS)-9-(2,6-dioxopiperidin-3-yl)-8-oxo-1,2,4a,5,9,10-hexahydro-8H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-3(4H)-yl)acetate
B343		1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl 2-(7-((S)-2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-c]isoindole-3,4'-piperidin]-1'-yl)acetate
B344		3-((4-(1-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione

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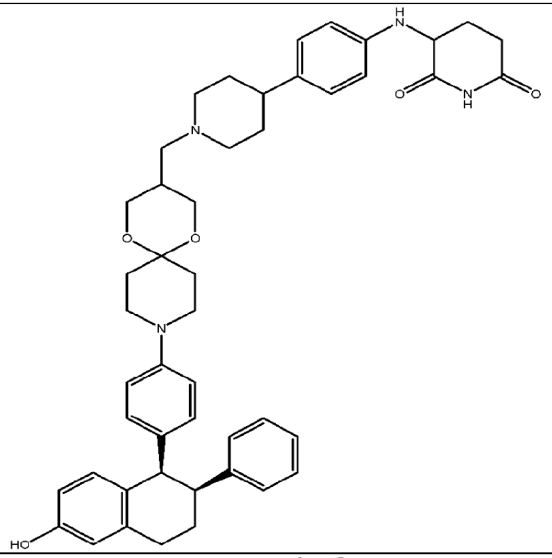
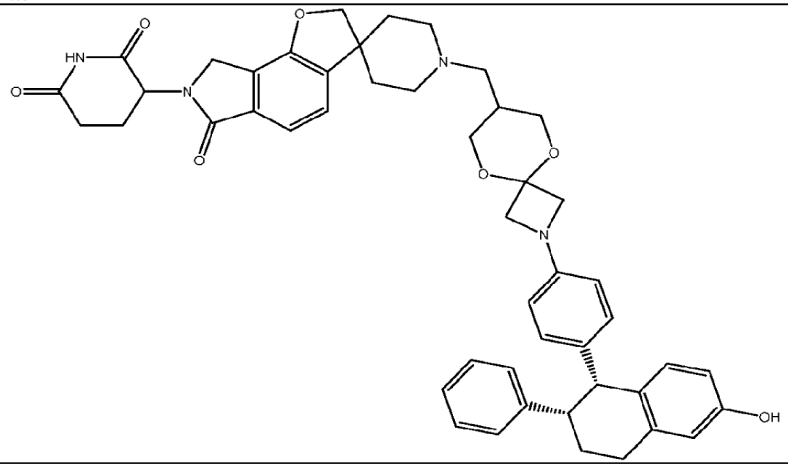
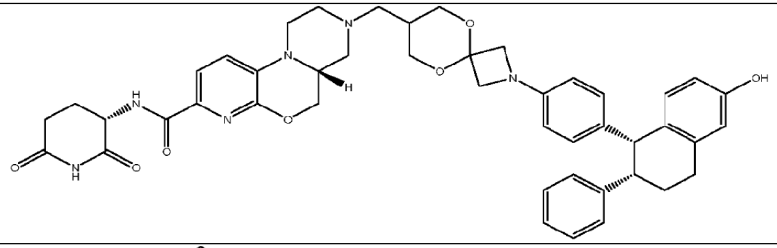
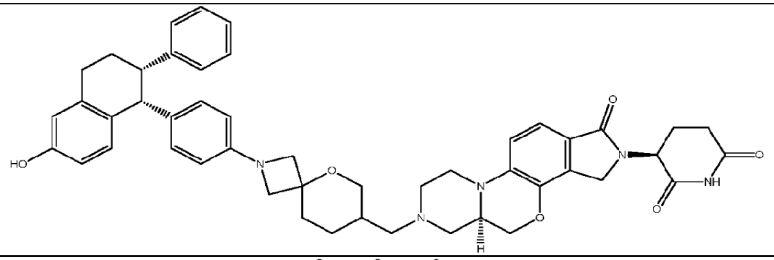
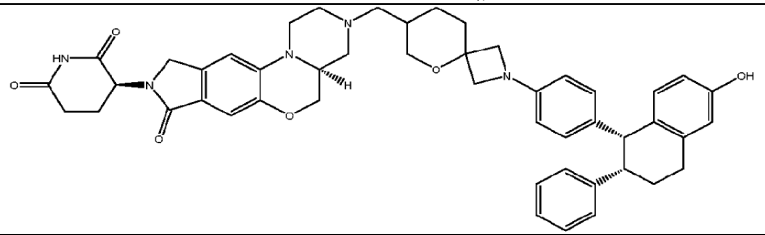
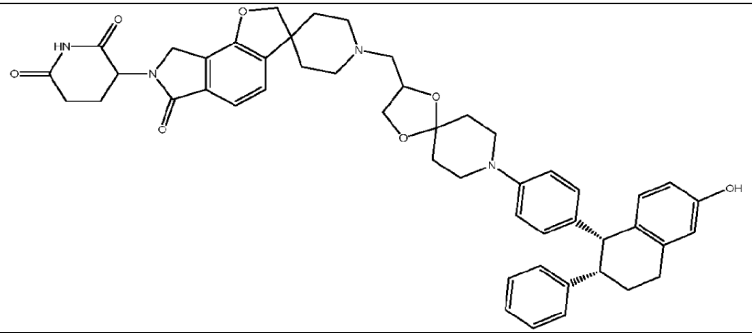
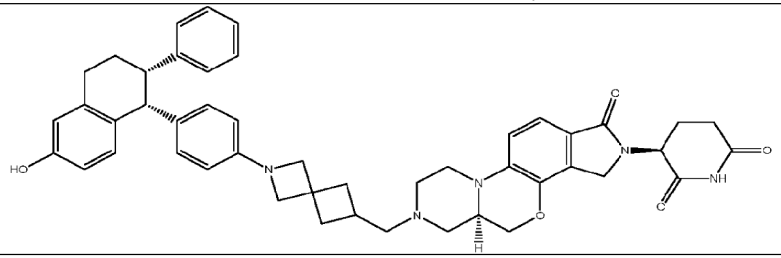
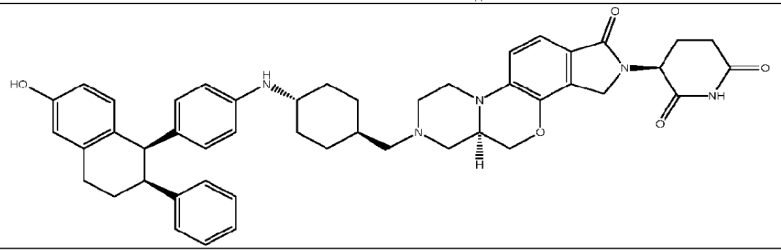
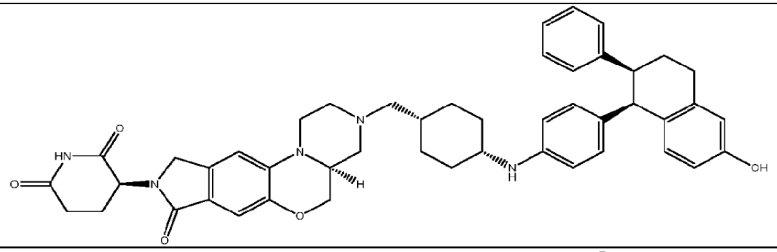
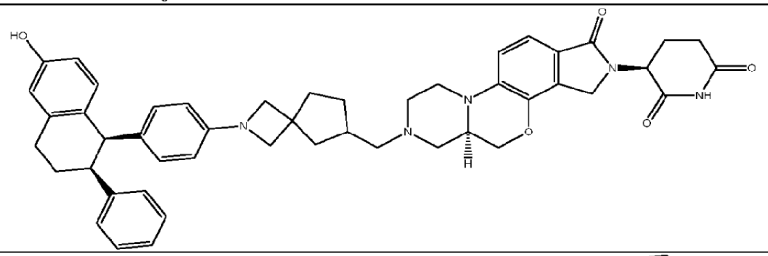
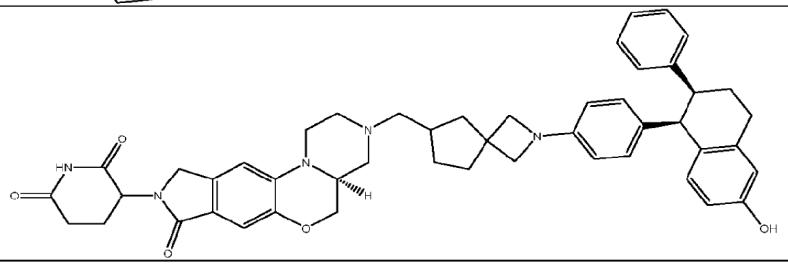
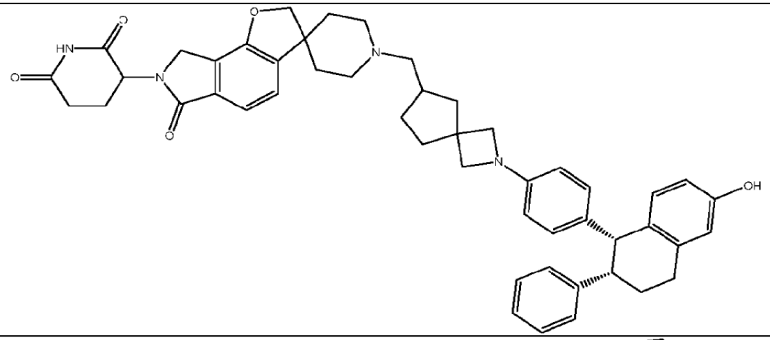
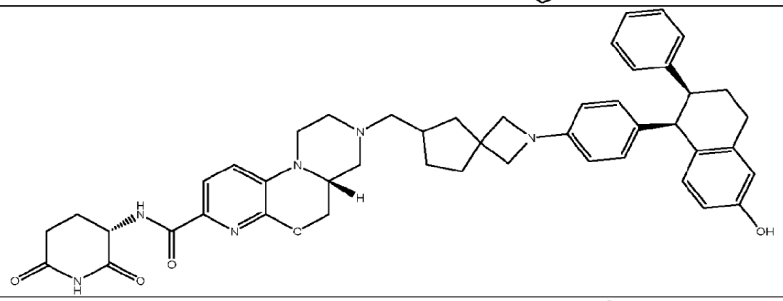
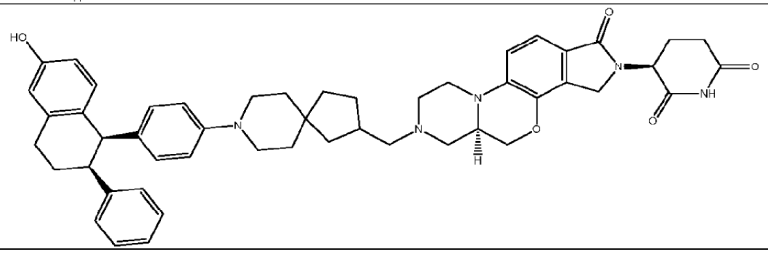
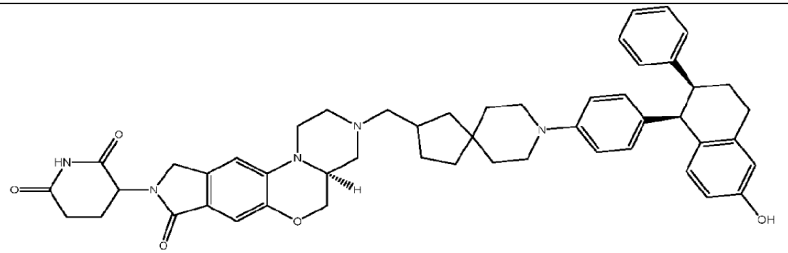
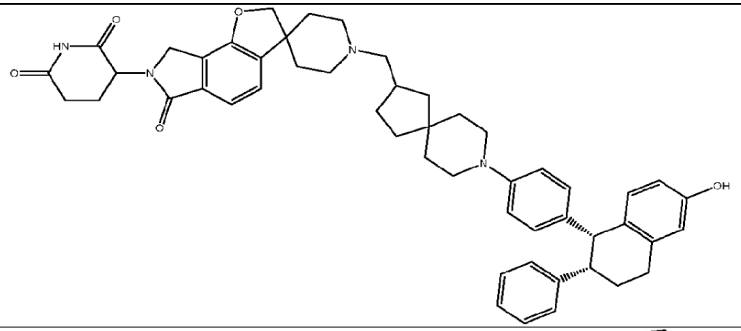
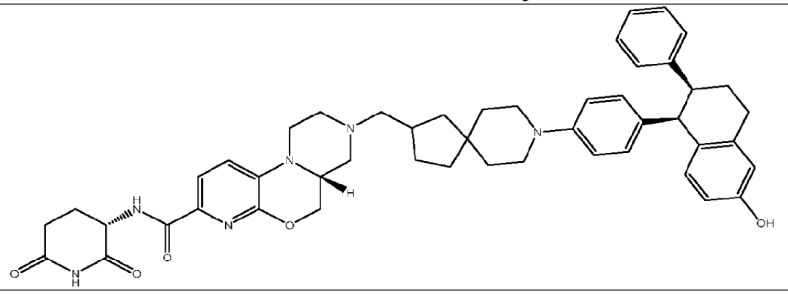
Compound No.	Chemical Structure	Chemical Name
B345		3-((4-(1-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
B346		3-(1'-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5,9-dioxa-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B347		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5,9-dioxa-2-azaspiro[3.5]nonan-7-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
B348		(3S)-3-((5aR)-7-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B349		(3S)-3-((4aS)-3-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B350		3-(1'-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,4-dioxa-8-azaspiro[4.5]decan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B351		(S)-3-((R)-7-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.3]heptan-6-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B353		(S)-3-((R)-7-(((1R,4R)-4-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)cyclohexyl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B354		(S)-3-((S)-3-(((1R,4S)-4-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)cyclohexyl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B357		(3S)-3-((5aR)-7-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.4]octan-6-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B358		3-((4aS)-3-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.4]octan-6-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B359		3-(1'-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.4]octan-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B360		(4aR)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.4]octan-6-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
B362		(3S)-3-((5aR)-7-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-8-azaspiro[4.5]decan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B363		3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-8-azaspiro[4.5]decan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B364		3-(1'-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-8-azaspiro[4.5]decan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B365		(4aR)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-8-azaspiro[4.5]decan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide

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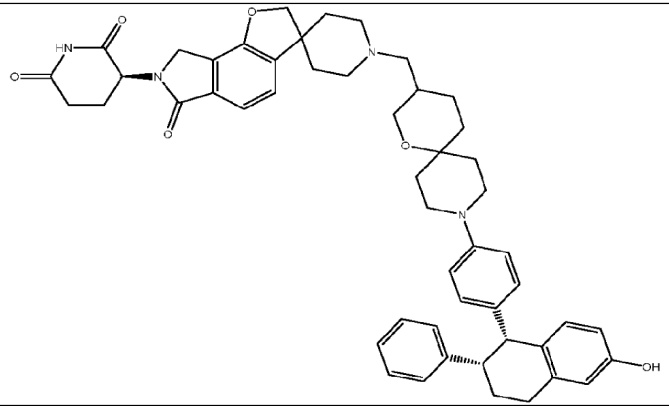
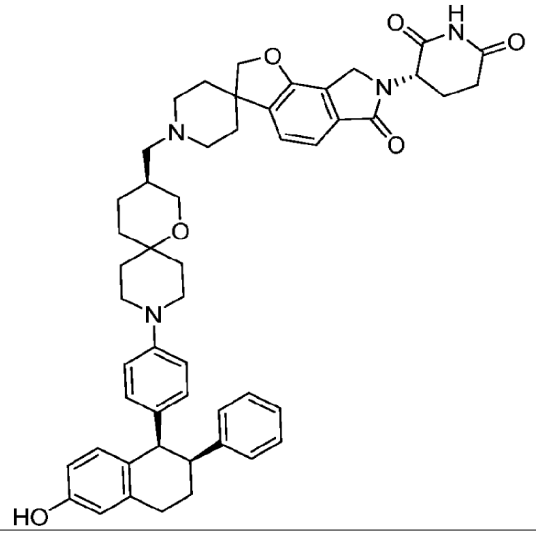
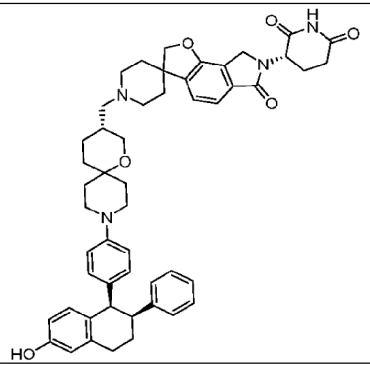
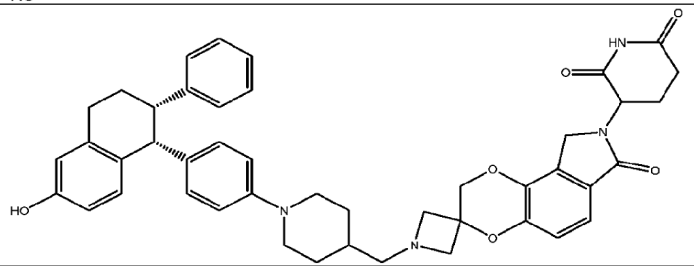
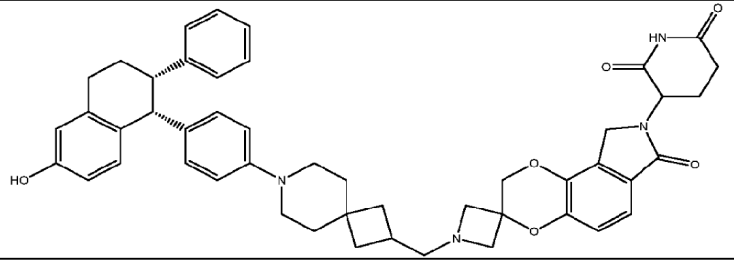
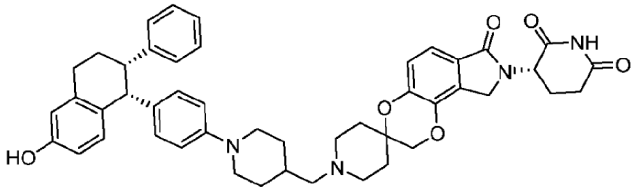
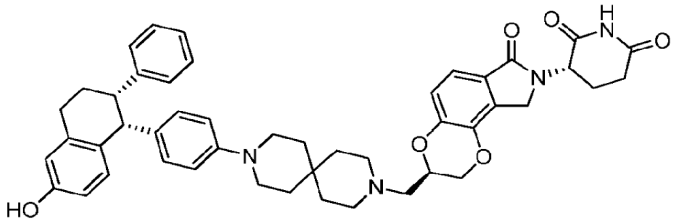
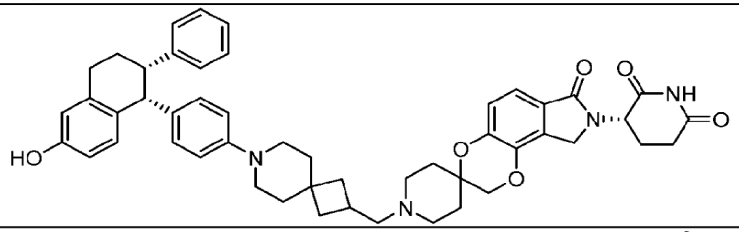
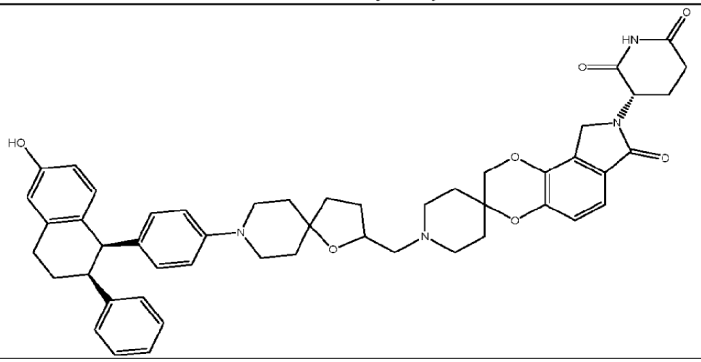
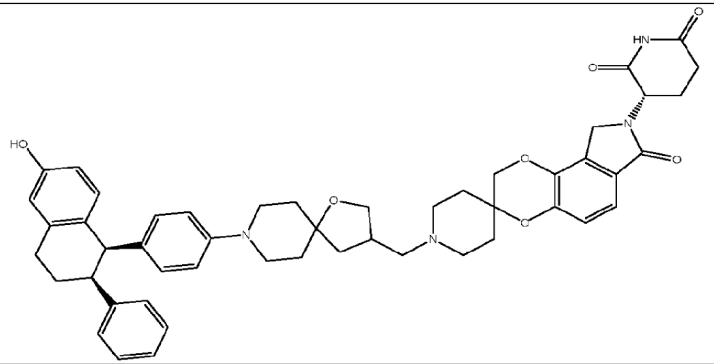
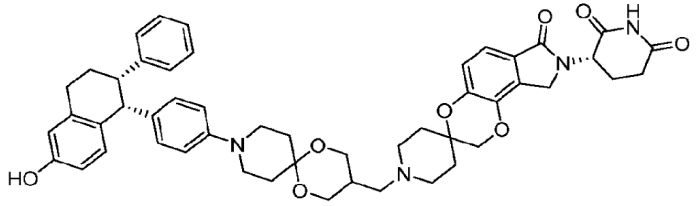
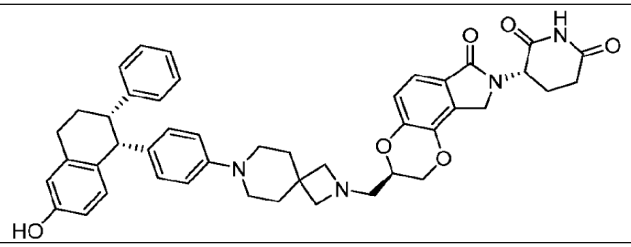
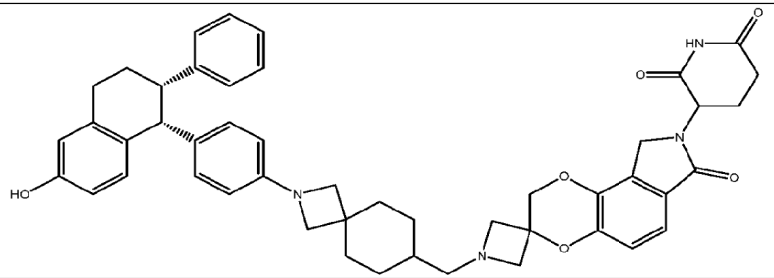
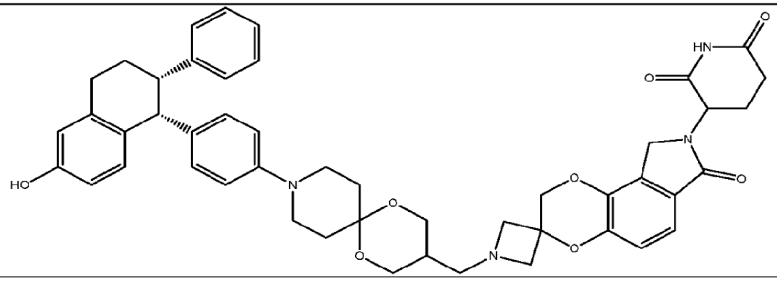
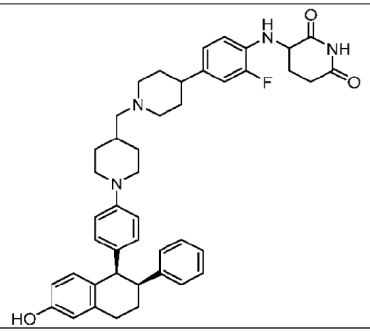
Compound No.	Chemical Structure	Chemical Name
B366		(3S)-3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B366X		(S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B366Y		(S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B367		3-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-7'-oxo-7',9'-dihydro-2'H,8'H-spiro[azetidine-3,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
B368		3-(1-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7'-oxo-7',9'-dihydro-2'H,8'H-spiro[azetidine-3,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B369		(S)-3-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-7'-oxo-7',9'-dihydro-2'H,8'H-spiro[piperidine-4,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
B370		(S)-3-((R)-3-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-7-oxo-2,3,7,9-tetrahydro-8H-[1,4]dioxino[2,3-e]isoindol-8-yl)piperidine-2,6-dione
B371		(S)-3-(1-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7'-oxo-7',9'-dihydro-2'H,8'H-spiro[piperidine-4,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
B372		(3S)-3-(1-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-2-yl)methyl)-7'-oxo-7',9'-dihydro-2'H,8'H-spiro[piperidine-4,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B373		(3S)-3-(1-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-7'-oxo-7',9'-dihydro-2'H,8'H-spiro[piperidine-4,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
B374		(S)-3-(1-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-7'-oxo-7',9'-dihydro-2'H,8'H-spiro[piperidine-4,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
B375		(S)-3-((R)-3-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)methyl)-7-oxo-2,3,7,9-tetrahydro-8H-[1,4]dioxino[2,3-e]isoindol-8-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B376		3-(1-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7'-oxo-7',9'-dihydro-2'H,8'H-spiro[azetidine-3,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
B377		3-(1-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-7'-oxo-7',9'-dihydro-2'H,8'H-spiro[azetidine-3,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
B378		3-((2-fluoro-4-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione

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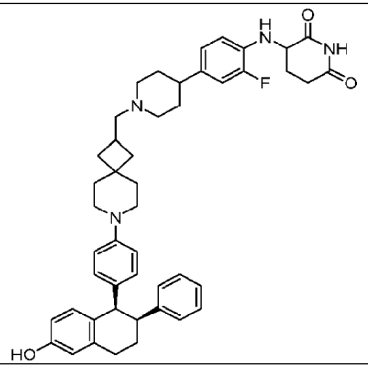
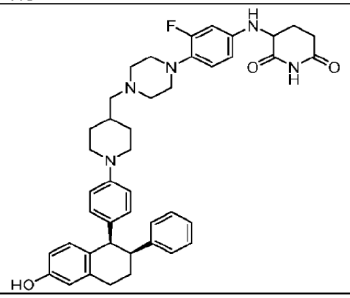
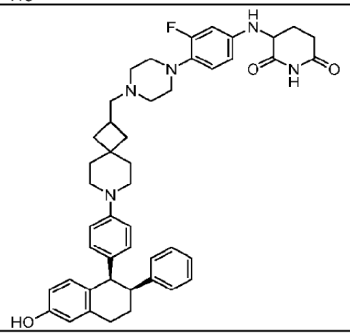
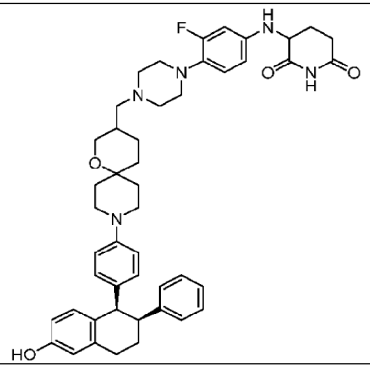
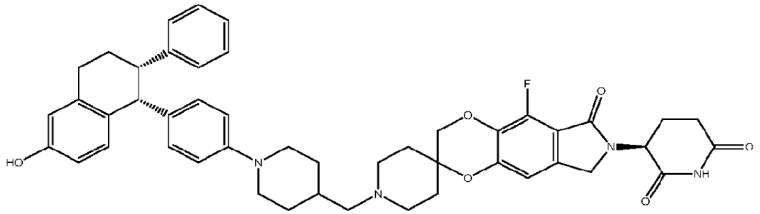
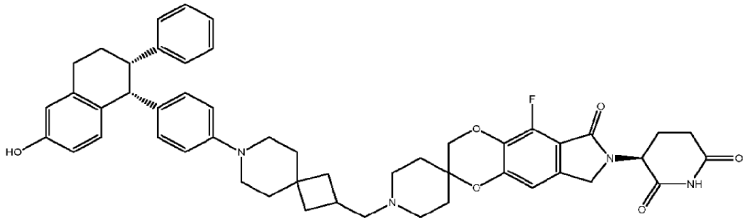
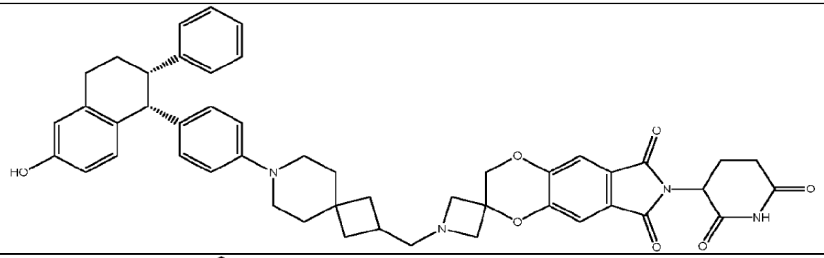
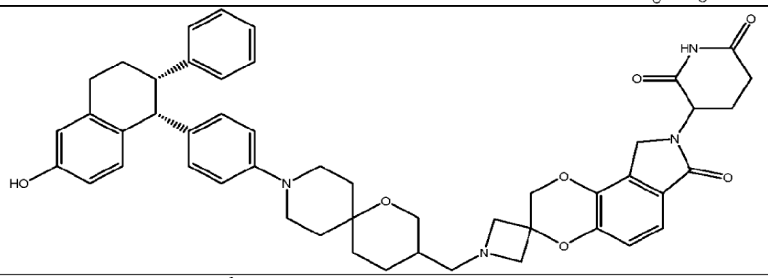
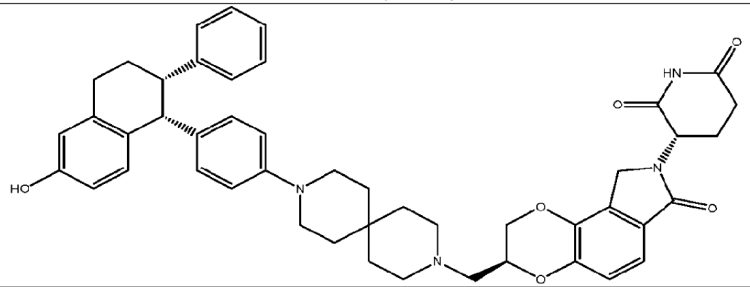
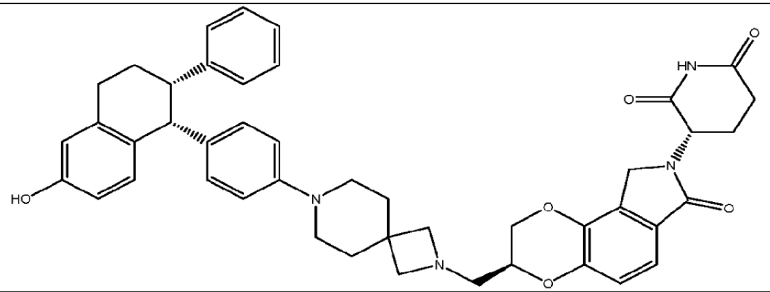
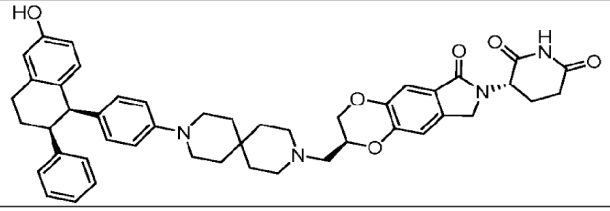
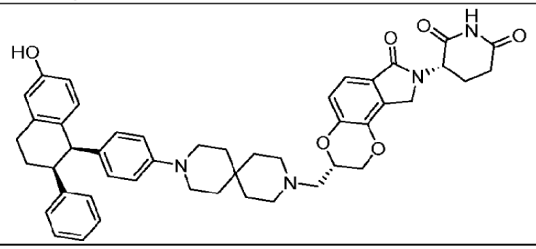
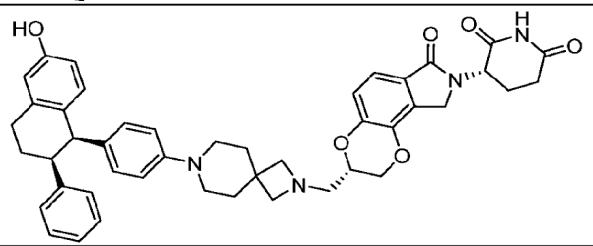
Compound No.	Chemical Structure	Chemical Name
B379		3-((2-fluoro-4-(1-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
B380		3-((3-fluoro-4-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenyl)amino)piperidine-2,6-dione
B381		3-((3-fluoro-4-(4-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)phenyl)amino)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B382		3-((3-fluoro-4-(4-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)piperazin-1-yl)phenyl)amino)piperidine-2,6-dione
B383		(S)-3-(5'-fluoro-1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-6'-oxo-6',8'-dihydro-3'H,7'H-spiro[piperidine-4,2'-[1,4]dioxino[2,3-f]isoindol]-7'-yl)piperidine-2,6-dione
B384		(S)-3-(5'-fluoro-1-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6'-oxo-6',8'-dihydro-3'H,7'H-spiro[piperidine-4,2'-[1,4]dioxino[2,3-f]isoindol]-7'-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B385		7'-(2,6-dioxopiperidin-3-yl)-1-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7'-hydro-3'H,6'H-spiro[azetidine-3,2'-[1,4]dioxino[2,3-f]isoindole]-6',8'-dione
B386		3-(1-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-7'-oxo-7',9'-dihydro-2'H,8'H-spiro[azetidine-3,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
B387		(S)-3-((S)-3-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-7-oxo-2,3,7,9-tetrahydro-8H-[1,4]dioxino[2,3-e]isoindol-8-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B388		(S)-3-((S)-3-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)methyl)-7-oxo-2,3,7,9-tetrahydro-8H-[1,4]dioxino[2,3-e]isoindol-8-yl)piperidine-2,6-dione
B391		(S)-3-((S)-2-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-6-oxo-2,3,6,8-tetrahydro-7H-[1,4]dioxino[2,3-f]isoindol-7-yl)piperidine-2,6-dione
B392		(S)-3-((S)-3-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-7-oxo-2,3,7,9-tetrahydro-8H-[1,4]dioxino[2,3-e]isoindol-8-yl)piperidine-2,6-dione
B393		(S)-3-((S)-3-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)methyl)-7-oxo-2,3,7,9-tetrahydro-8H-[1,4]dioxino[2,3-e]isoindol-8-yl)piperidine-2,6-dione

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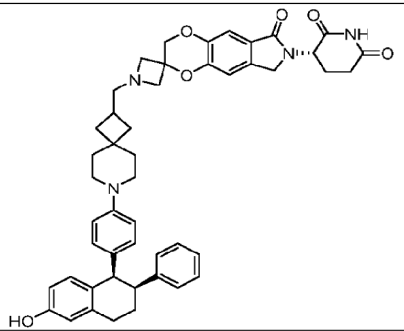
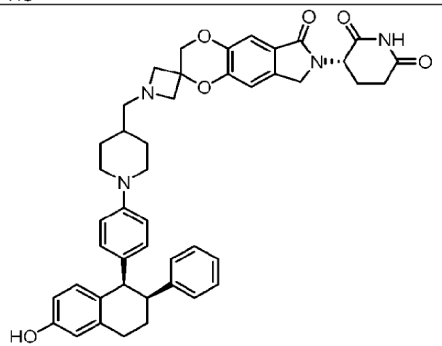
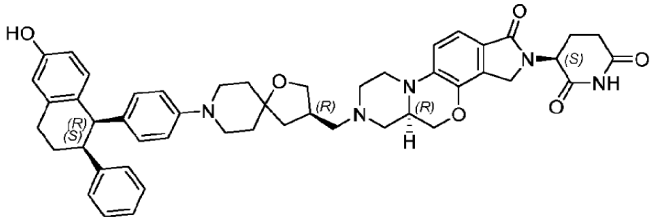
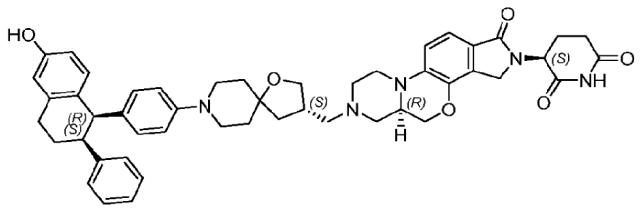
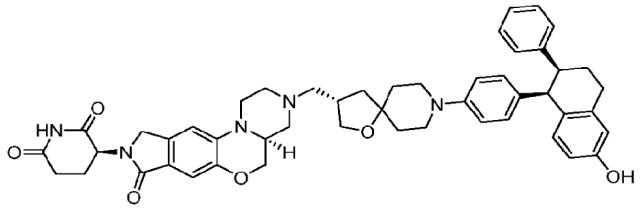
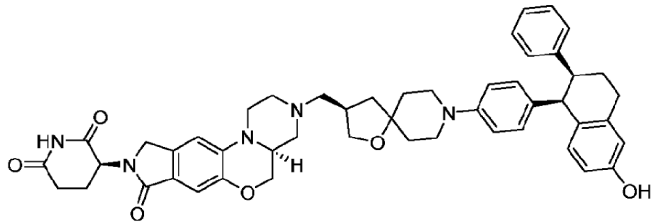
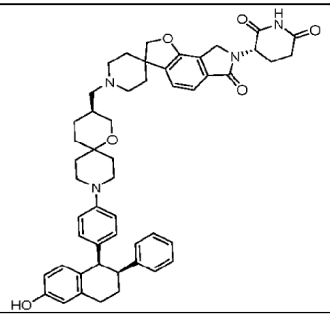
Compound No.	Chemical Structure	Chemical Name
B394		(S)-3-(1-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6'-oxo-6',8'-dihydro-3'H,7'H-spiro[azetidine-3,2'-[1,4]dioxino[2,3-f]isoindol]-7'-yl)piperidine-2,6-dione
B395		(S)-3-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-6'-oxo-6',8'-dihydro-3'H,7'H-spiro[azetidine-3,2'-[1,4]dioxino[2,3-f]isoindol]-7'-yl)piperidine-2,6-dione
B396		(S)-3-((R)-7-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B397		(S)-3-((R)-7-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B398		(S)-3-((S)-3-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B399		(S)-3-((S)-3-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B400		(S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

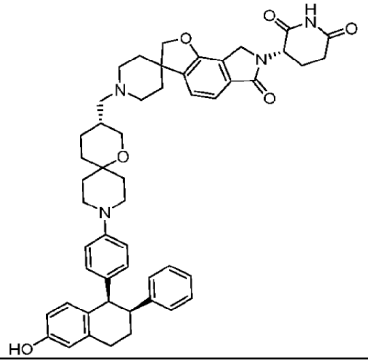
Compound No.	Chemical Structure	Chemical Name
B401		(S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

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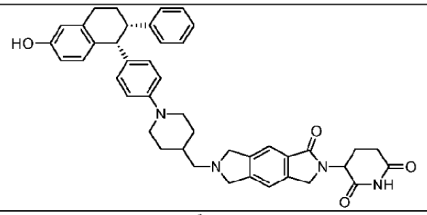
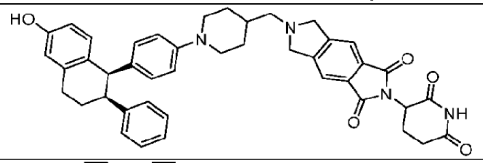
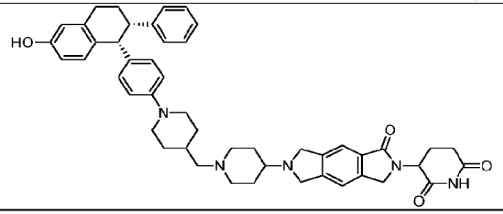
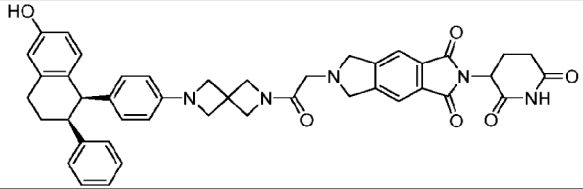
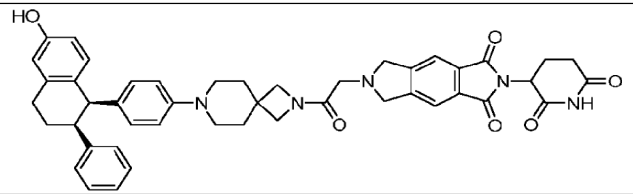
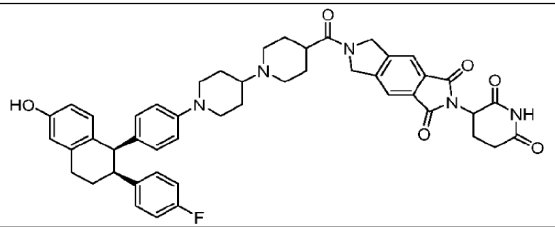
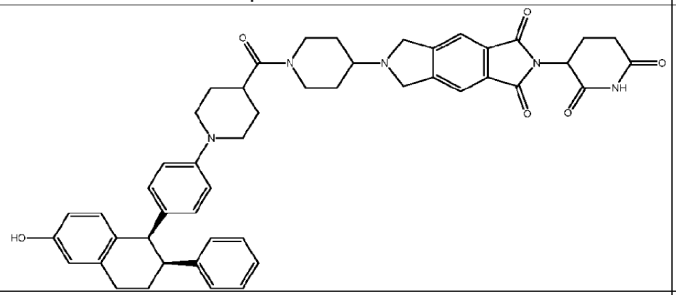
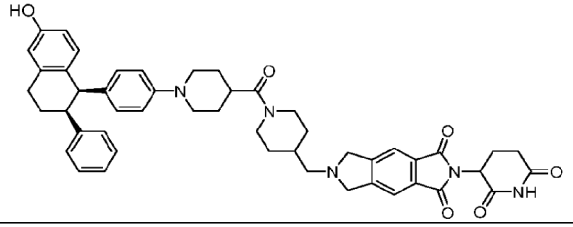
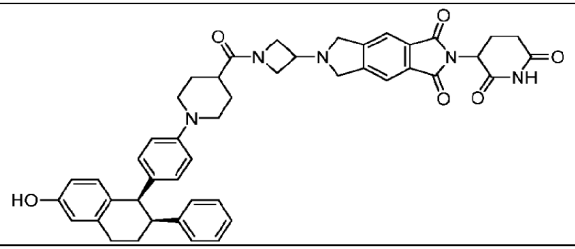
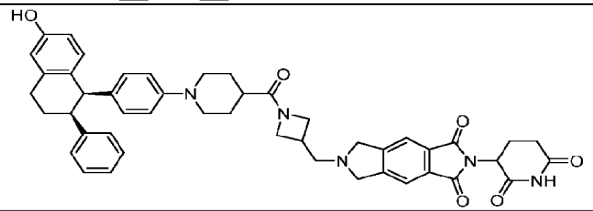
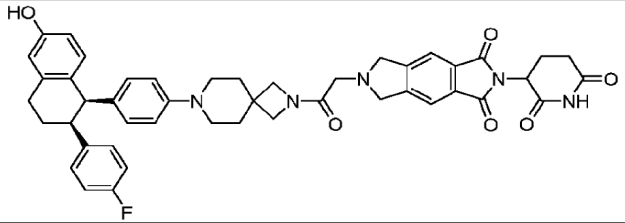
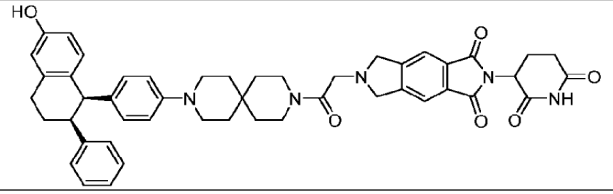
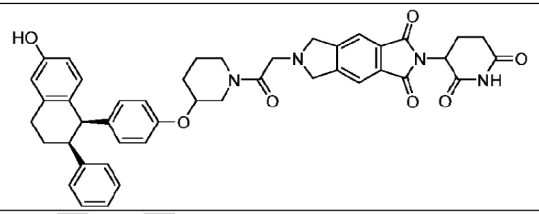
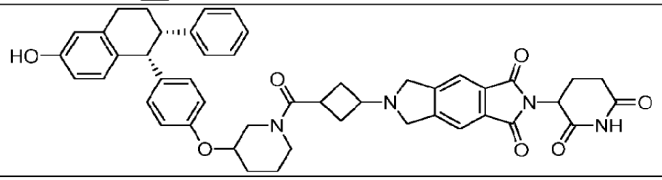
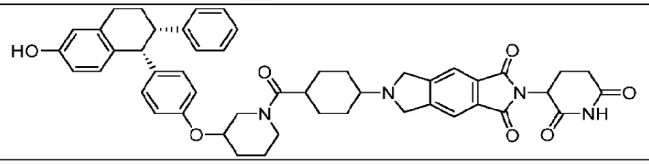
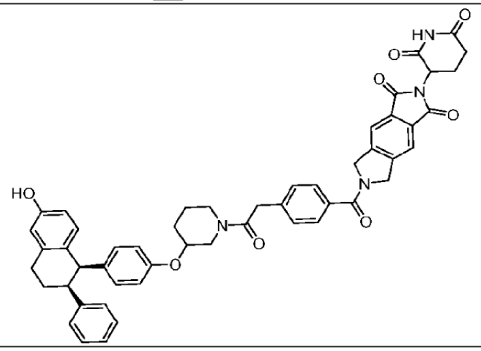
Table 3.

designates that it is racemic with respect to the two stereogenic centers at the warhead (tetrahydronaphthalene); the relative configuration of the two stereogenic center is **cis.*

Compound No.	Chemical Structure	Chemical Name
B1*		3-(6-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B2*		2-(2,6-dioxopiperidin-3-yl)-6-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B3*		3-(6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B4*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(6-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.3]heptan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B5*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B6*		2-(2,6-dioxopiperidin-3-yl)-6-(1'-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B7		2-(2,6-dioxopiperidin-3-yl)-6-(1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine-4-carbonyl)piperidin-4-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B8*		2-(2,6-dioxopiperidin-3-yl)-6-((1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine-4-carbonyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B9*		2-(2,6-dioxopiperidin-3-yl)-6-(1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine-4-carbonyl)azetidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B10*		2-(2,6-dioxopiperidin-3-yl)-6-((1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine-4-carbonyl)azetidin-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B11*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B12*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B13*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)piperidin-1-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B14*		2-(2,6-dioxopiperidin-3-yl)-6-(3-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)piperidine-1-carbonyl)cyclobutyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B15*		2-(2,6-dioxopiperidin-3-yl)-6-(4-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)piperidine-1-carbonyl)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B16		2-(2,6-dioxopiperidin-3-yl)-6-(4-(2-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)piperidin-1-yl)-2-oxoethyl)benzoyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

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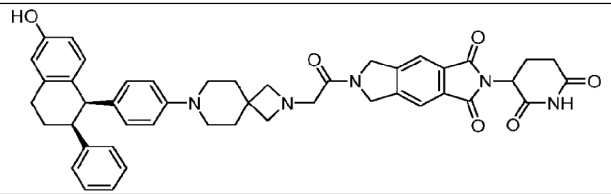
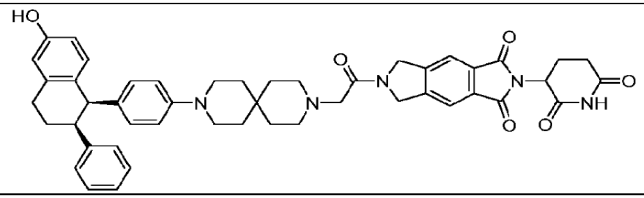
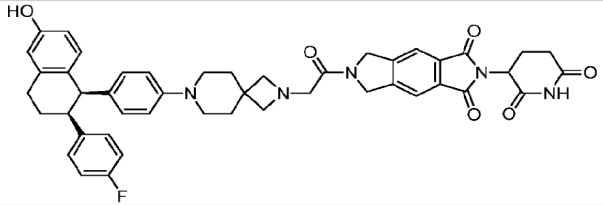
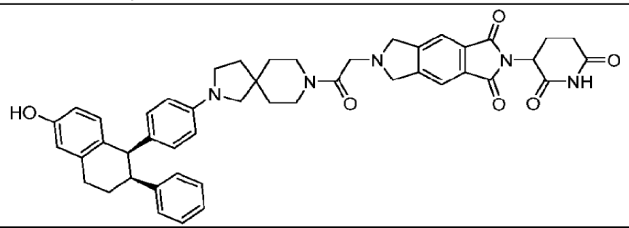
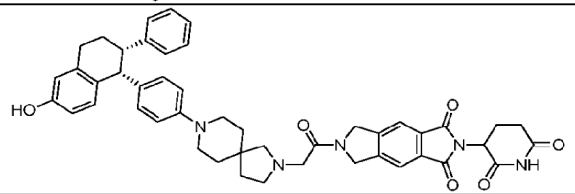
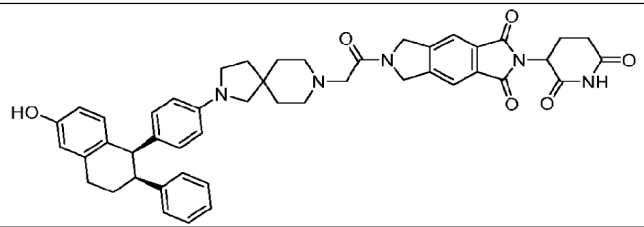
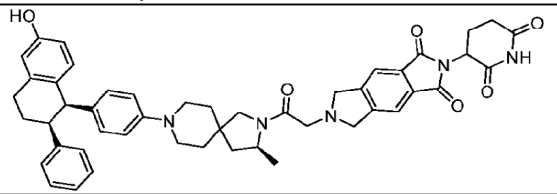
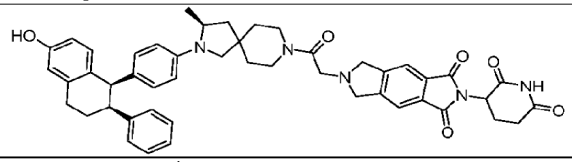
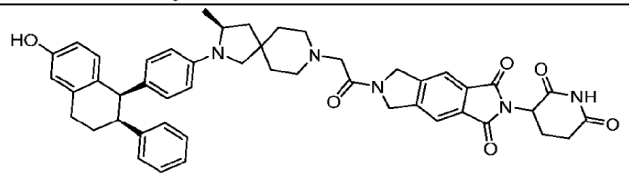
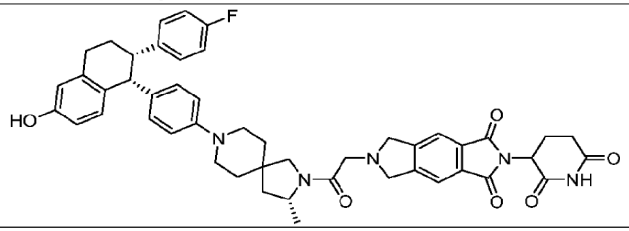
Compound No.	Chemical Structure	Chemical Name
B17*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B18*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B19*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B20*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,8-diazaspiro[4.5]decan-8-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B21*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,8-diazaspiro[4.5]decan-2-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B22*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,8-diazaspiro[4.5]decan-8-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B23*		2-(2,6-dioxopiperidin-3-yl)-6-(2-((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-methyl-2,8-diazaspiro[4.5]decan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B24*		2-(2,6-dioxopiperidin-3-yl)-6-(2-((S)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-methyl-2,8-diazaspiro[4.5]decan-8-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B25*		2-(2,6-dioxopiperidin-3-yl)-6-(2-((S)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-methyl-2,8-diazaspiro[4.5]decan-8-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B26*		2-(2,6-dioxopiperidin-3-yl)-6-(2-((R)-8-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-methyl-2,8-diazaspiro[4.5]decan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

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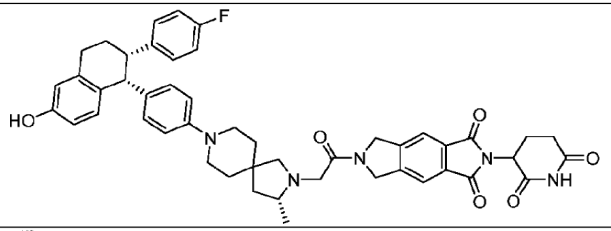
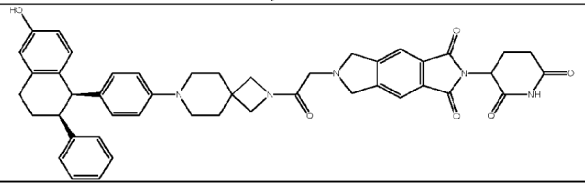
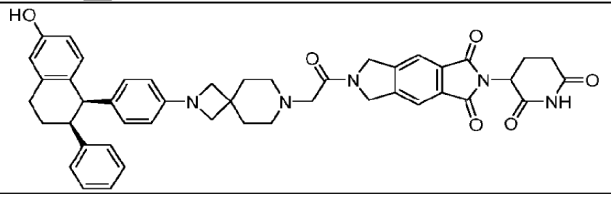
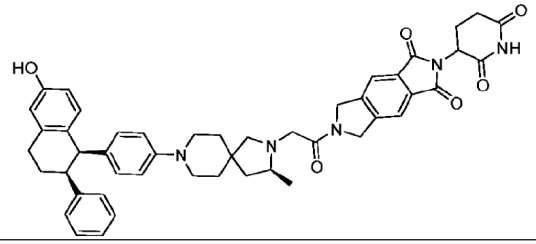
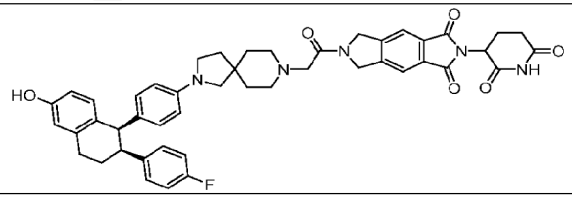
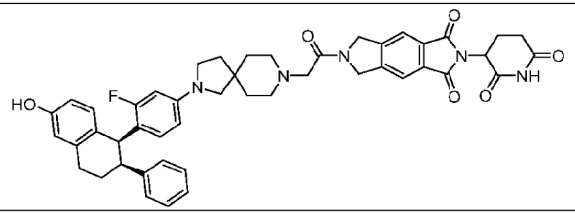
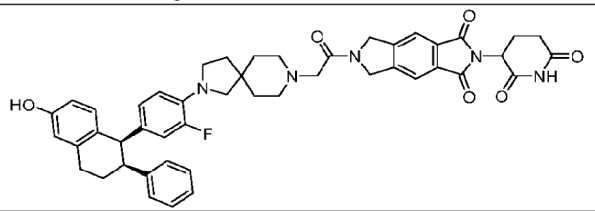
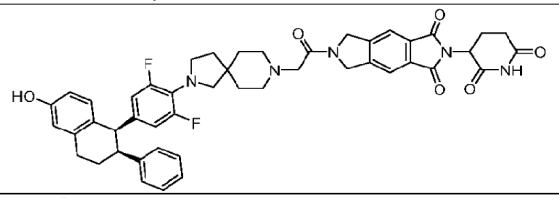
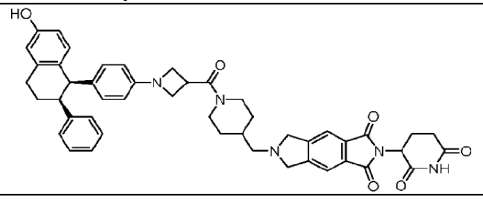
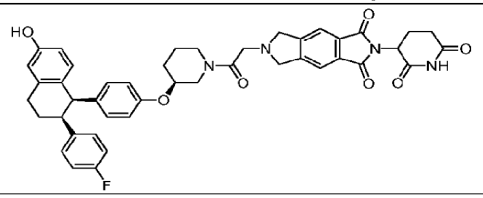
B27*		2-(2,6-dioxopiperidin-3-yl)-6-(2-((R)-8-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-methyl-2,8-diazaspiro[4.5]decan-2-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B28		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B29*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B30*		2-(2,6-dioxopiperidin-3-yl)-6-(2-((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-methyl-2,8-diazaspiro[4.5]decan-2-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B31*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,8-diazaspiro[4.5]decan-8-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B32*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(3-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,8-diazaspiro[4.5]decan-8-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B33*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,8-diazaspiro[4.5]decan-8-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B34*		6-(2-(2-(2,6-difluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,8-diazaspiro[4.5]decan-8-yl)acetyl)-2-(2,6-dioxopiperidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B35*		2-(2,6-dioxopiperidin-3-yl)-6-((1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidine-3-carbonyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B36*		2-(2,6-dioxopiperidin-3-yl)-6-(2-((S)-3-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)piperidin-1-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

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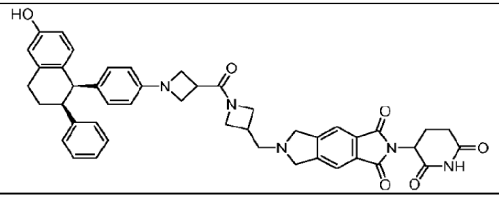
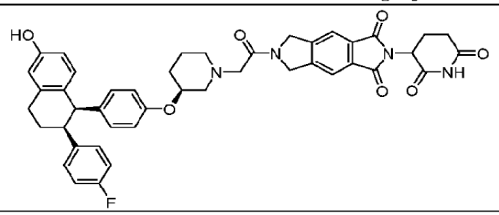
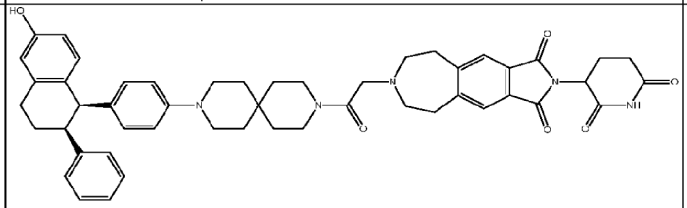
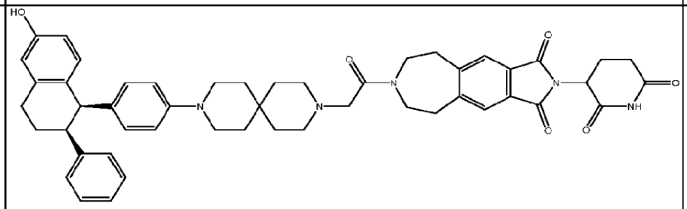
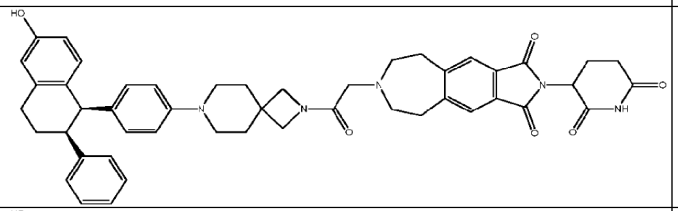
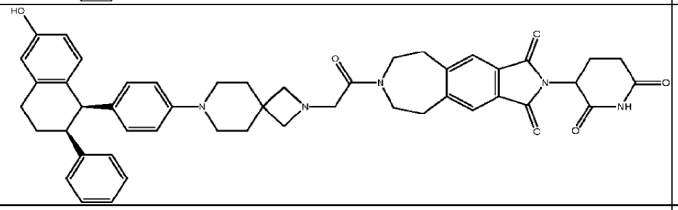
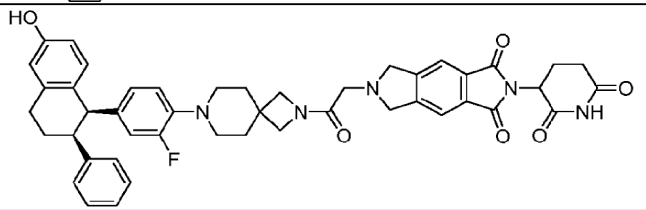
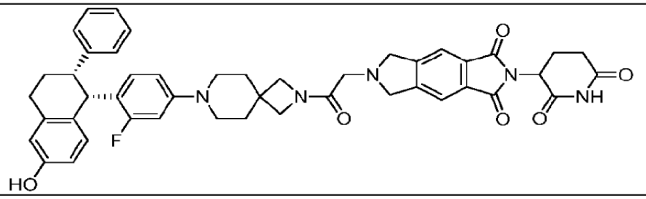
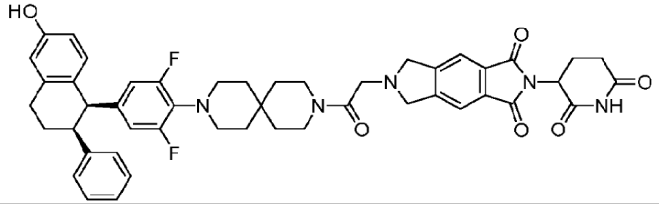
B37*		2-(2,6-dioxopiperidin-3-yl)-6-((1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidine-3-carbonyl)azetidin-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B38*		2-(2,6-dioxopiperidin-3-yl)-6-(2-((S)-3-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)piperidin-1-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B39		2-(2,6-dioxopiperidin-3-yl)-7-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7,8,9-tetrahydroazepino[4,5-f]isoindole-1,3(2H,5H)-dione
B40		2-(2,6-dioxopiperidin-3-yl)-7-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-6,7,8,9-tetrahydroazepino[4,5-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B41		2-(2,6-dioxopiperidin-3-yl)-7-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7,8,9-tetrahydroazepino[4,5-f]isoindole-1,3(2H,5H)-dione
B42		2-(2,6-dioxopiperidin-3-yl)-7-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-6,7,8,9-tetrahydroazepino[4,5-f]isoindole-1,3(2H,5H)-dione
B43*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B44*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(3-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B45*		6-(2-(9-(2,6-difluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-2-(2,6-dioxopiperidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

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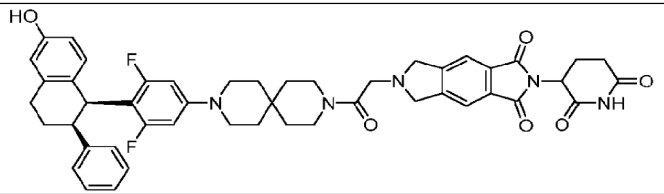
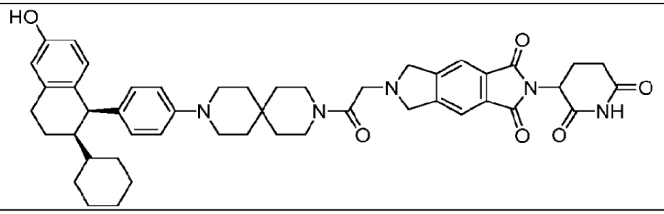
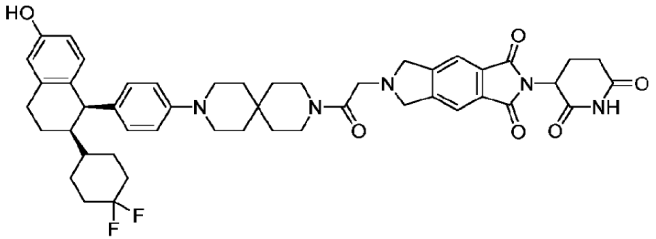
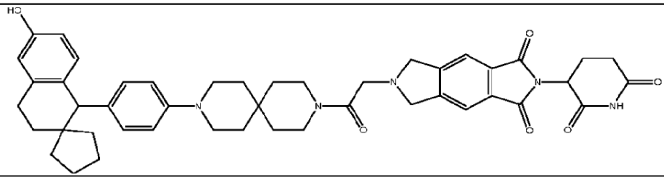
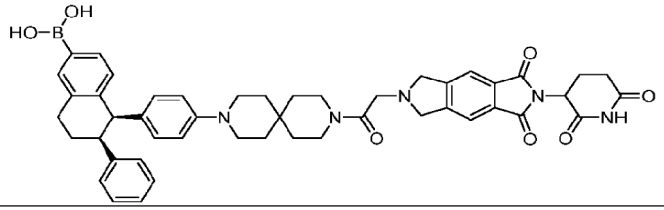
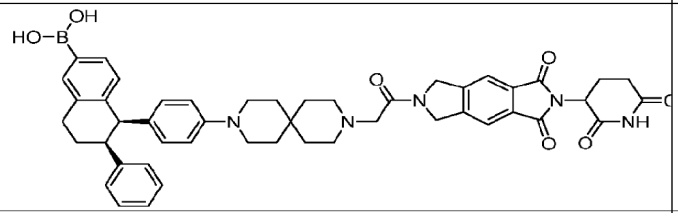
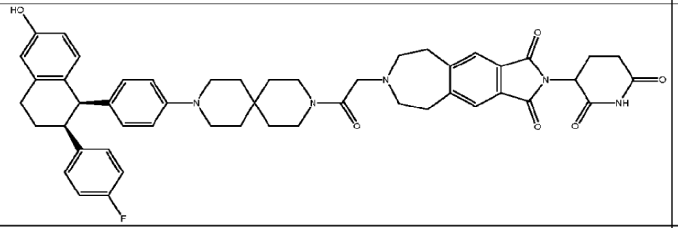
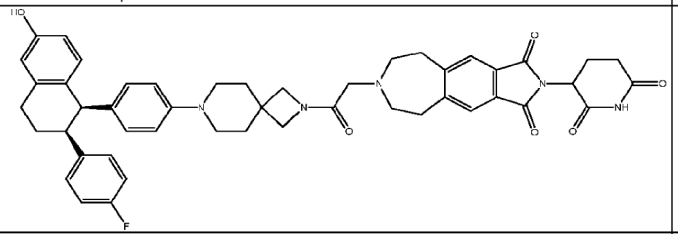
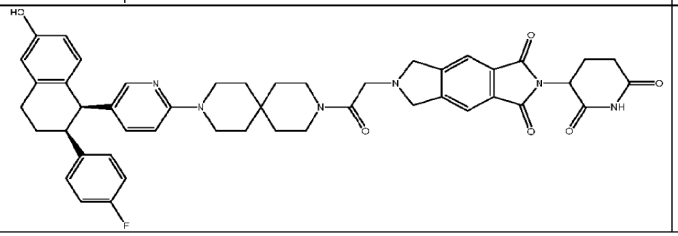
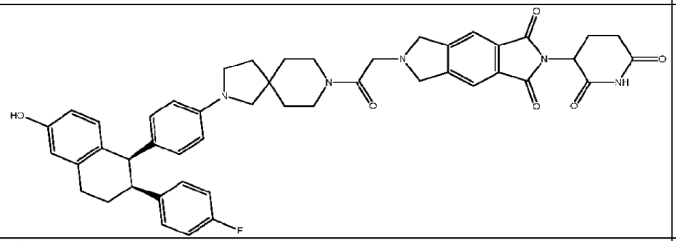
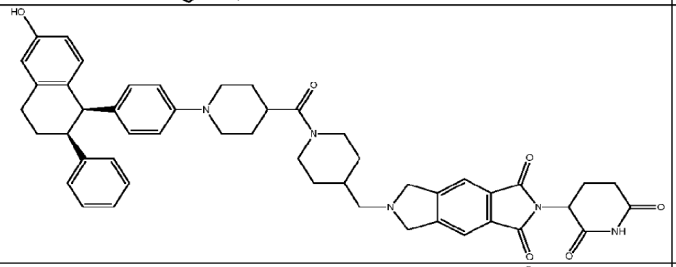
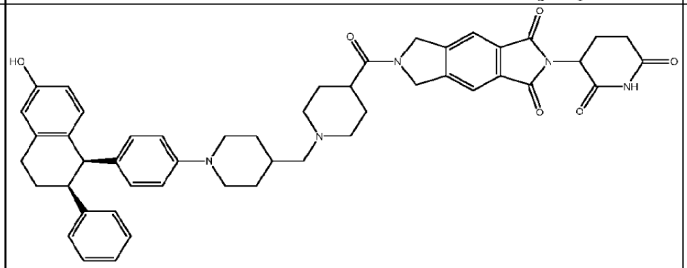
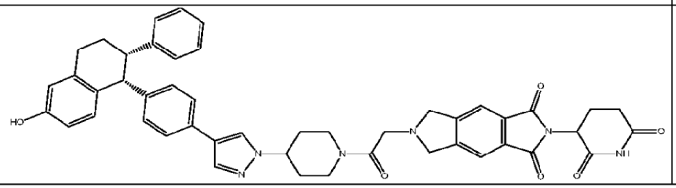
Compound No.	Chemical Structure	Chemical Name
B46*		6-(2-(9-(3,5-difluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-2-(2,6-dioxopiperidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B47*		6-(2-(9-(4-((1R,2R)-2-cyclohexyl-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-2-(2,6-dioxopiperidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B48*		6-(2-(9-(4-((1R,2R)-2-(4,4-difluorocyclohexyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-2-(2,6-dioxopiperidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B49		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-(6'-hydroxy-3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-naphthalen]-1'-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B50*		((5R,6S)-5-(4-(9-(2-(6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)acetyl)-3,9-diazaspiro[5.5]undecan-3-yl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-yl)boronic acid

Compound No.	Chemical Structure	Chemical Name
B51*		((5R,6S)-5-(4-(9-(2-(6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)-2-oxoethyl)-3,9-diazaspiro[5.5]undecan-3-yl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-yl)boronic acid
B52		2-(2,6-dioxopiperidin-3-yl)-7-(2-(9-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7,8,9-tetrahydroazepino[4,5-f]isoindole-1,3(2H,5H)-dione
B53		2-(2,6-dioxopiperidin-3-yl)-7-(2-(7-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7,8,9-tetrahydroazepino[4,5-f]isoindole-1,3(2H,5H)-dione
B54		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(5-((1S,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B55		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,8-diazaspiro[4.5]decan-8-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B56		2-(2,6-dioxopiperidin-3-yl)-6-((1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine-4-carbonyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B57		2-(2,6-dioxopiperidin-3-yl)-6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidine-4-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B58		2-(2,6-dioxopiperidin-3-yl)-6-(2-(4-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1H-pyrazol-1-yl)piperidin-1-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

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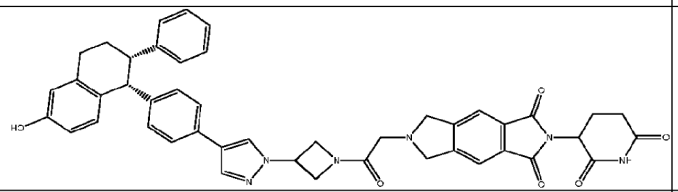
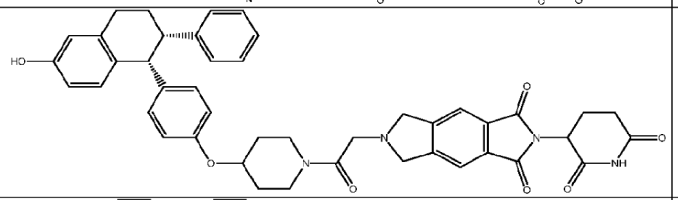
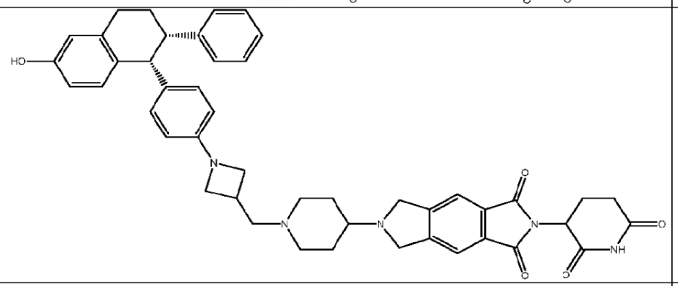
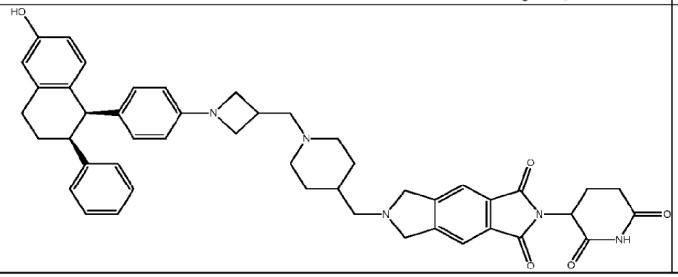
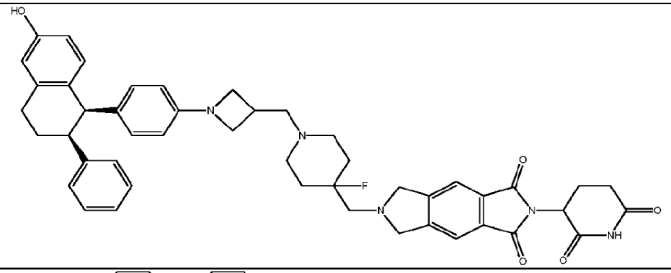
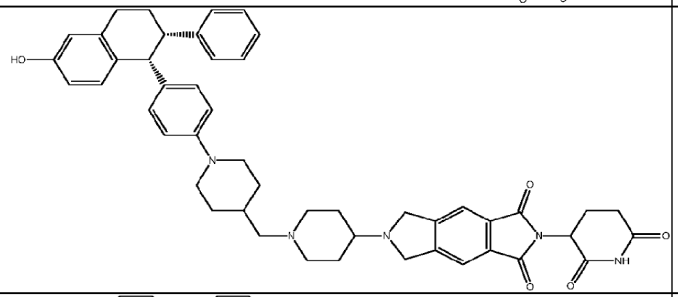
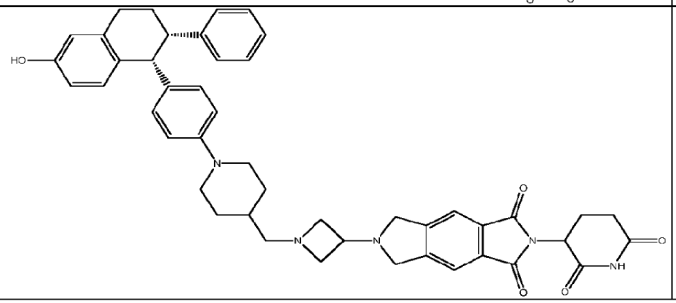
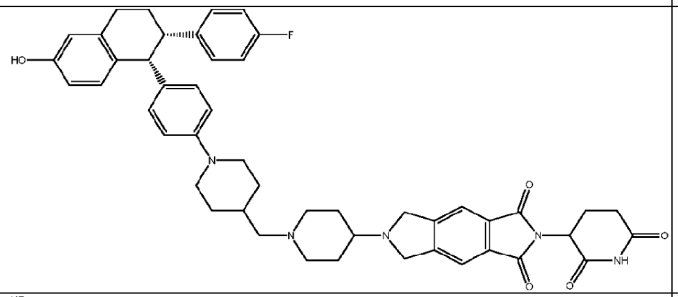
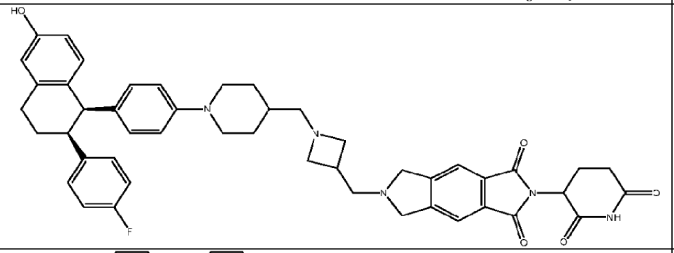
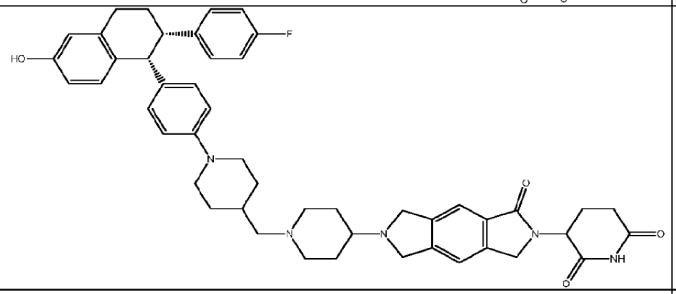
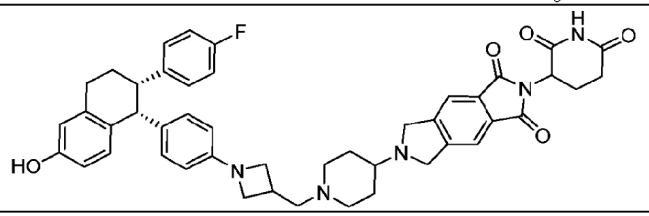
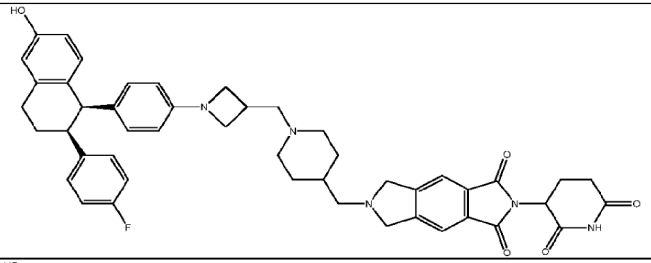
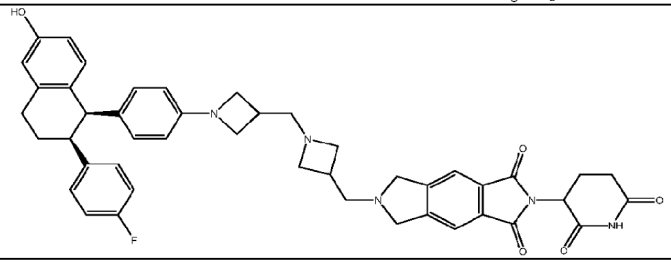
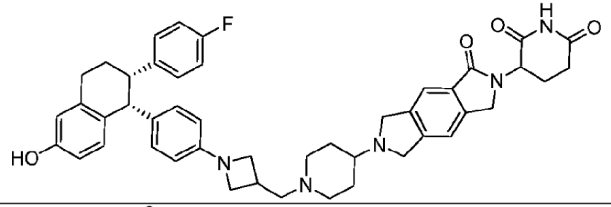
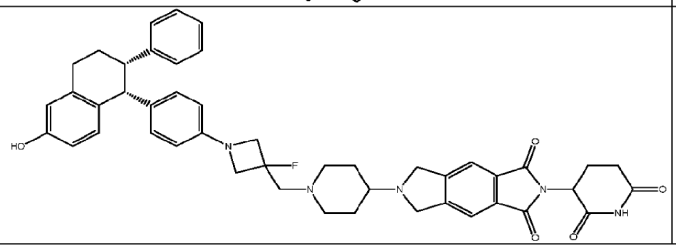
Compound No.	Chemical Structure	Chemical Name
B59		2-(2,6-dioxopiperidin-3-yl)-6-(2-(3-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1H-pyrazol-1-yl)azetidin-1-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B60		2-(2,6-dioxopiperidin-3-yl)-6-(2-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)piperidin-1-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B61		2-(2,6-dioxopiperidin-3-yl)-6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B62		2-(2,6-dioxopiperidin-3-yl)-6-((1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B63		2-(2,6-dioxopiperidin-3-yl)-6-((4-fluoro-1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B64		2-(2,6-dioxopiperidin-3-yl)-6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B65		2-(2,6-dioxopiperidin-3-yl)-6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B66		2-(2,6-dioxopiperidin-3-yl)-6-(1-((1-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B67		2-(2,6-dioxopiperidin-3-yl)-6-((1-((1-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B68		3-(6-(1-((1-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B69		2-(2,6-dioxopiperidin-3-yl)-6-(1-((1-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B70		2-(2,6-dioxopiperidin-3-yl)-6-((1-((1-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B71		2-(2,6-dioxopiperidin-3-yl)-6-((1-((1-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)azetidin-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B72		3-(6-(1-((1-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B73		2-(2,6-dioxopiperidin-3-yl)-6-(1-((3-fluoro-1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

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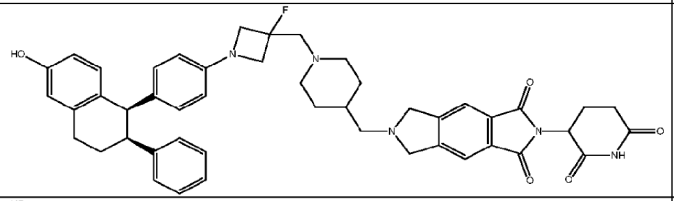
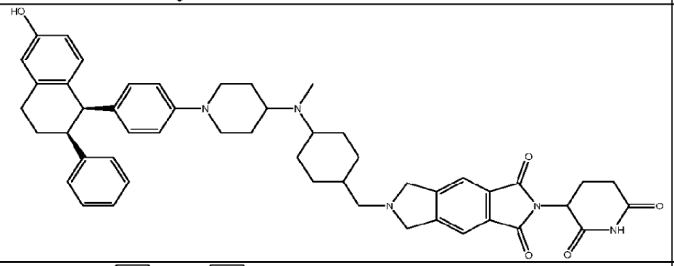
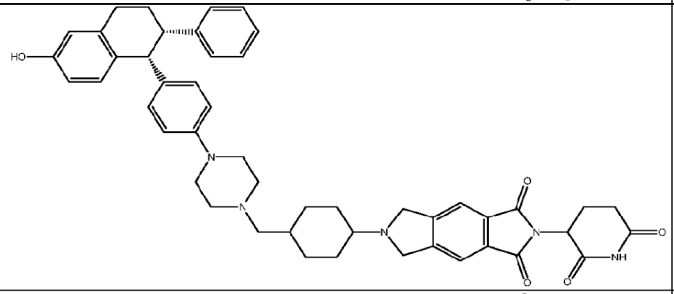
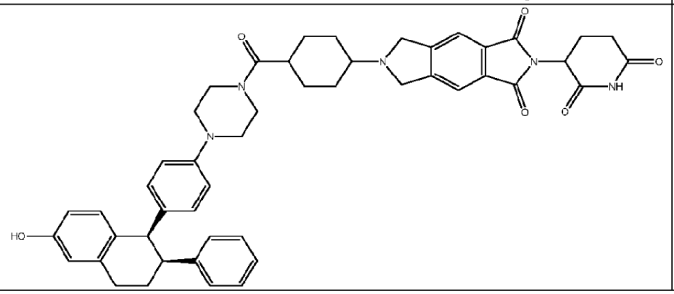
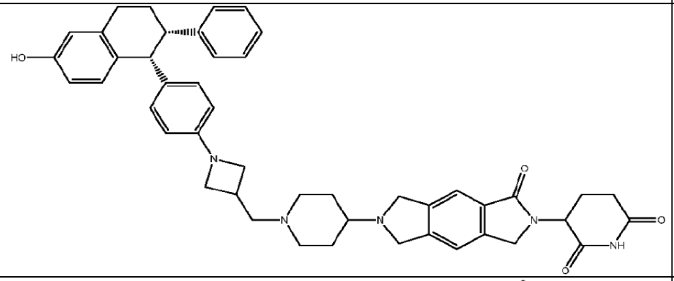
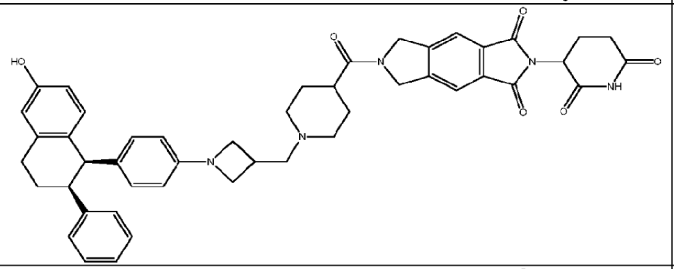
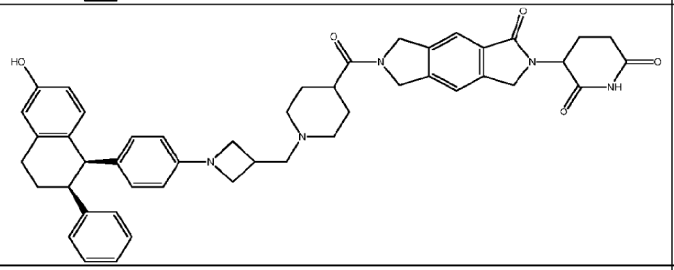
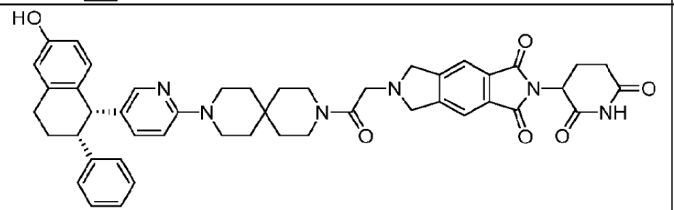
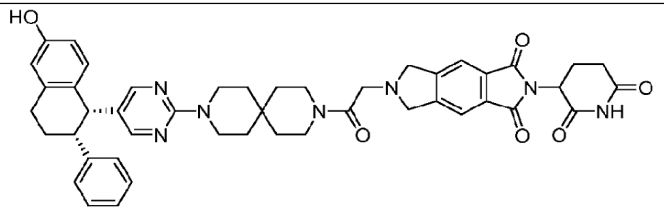
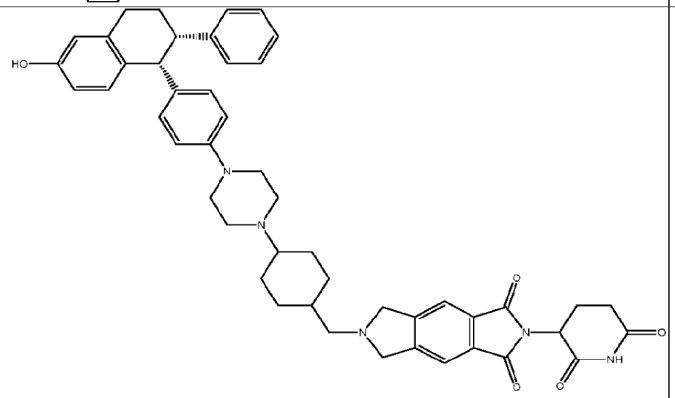
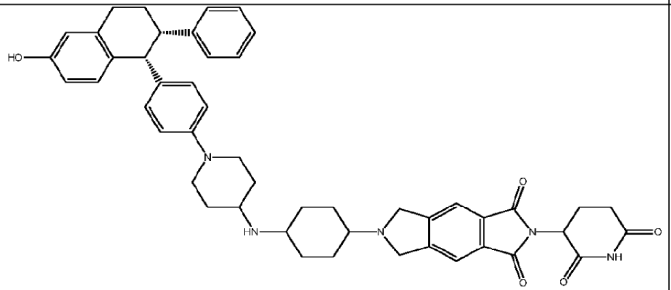
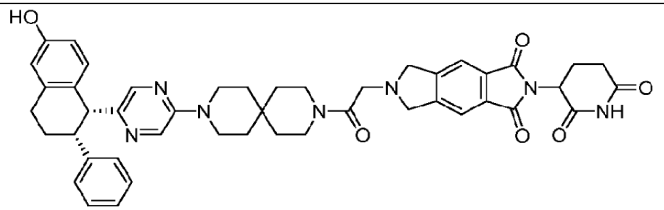
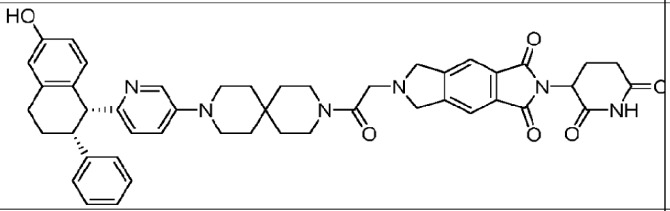
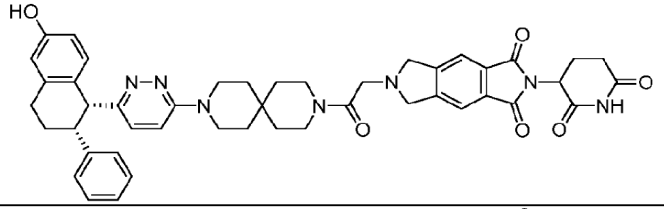
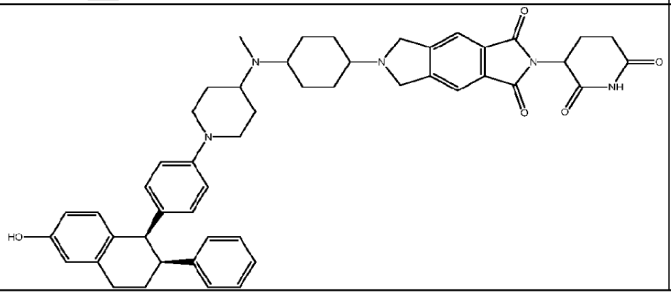
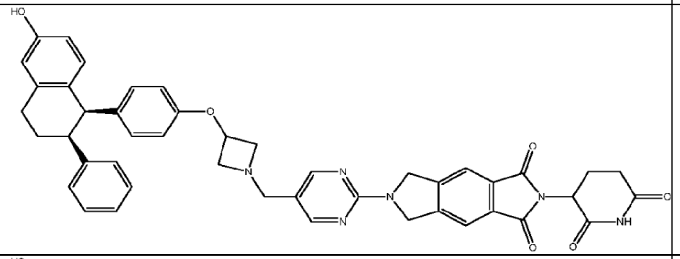
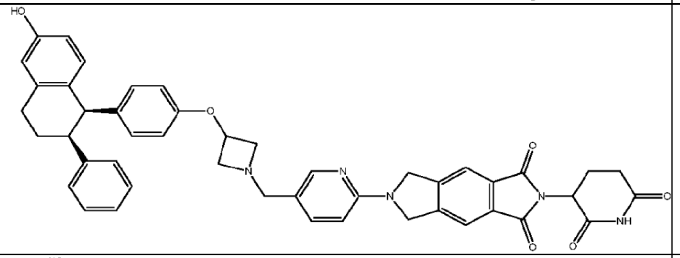
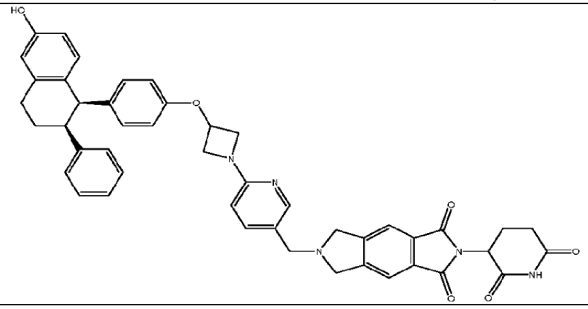
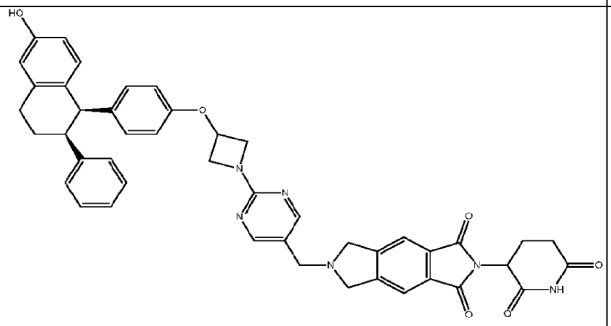
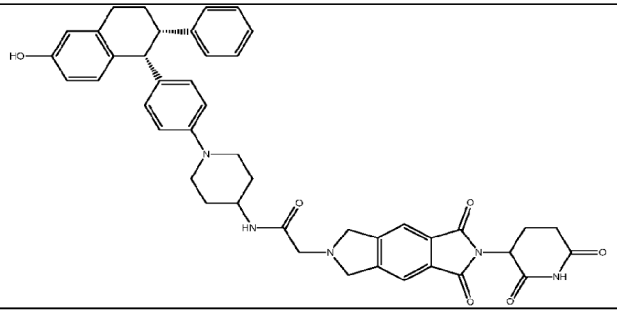
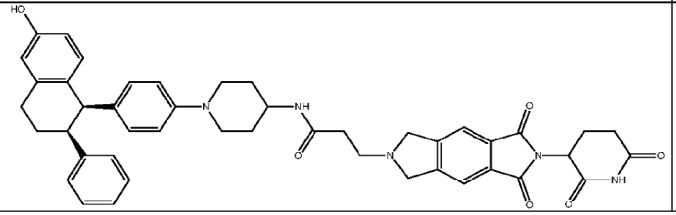
Compound No.	Chemical Structure	Chemical Name
B74		2-(2,6-dioxopiperidin-3-yl)-6-((1-((3-fluoro-1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B75		2-(2,6-dioxopiperidin-3-yl)-6-((4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)(methyl)amino)cyclohexyl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B76		2-(2,6-dioxopiperidin-3-yl)-6-(4-((4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)methyl)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B77		2-(2,6-dioxopiperidin-3-yl)-6-(4-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazine-1-carbonyl)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

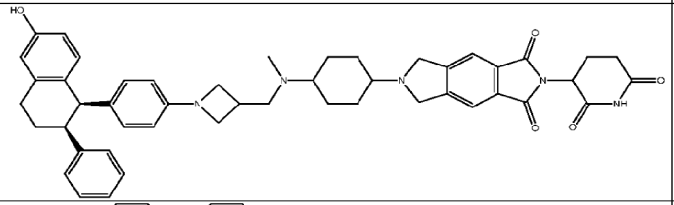
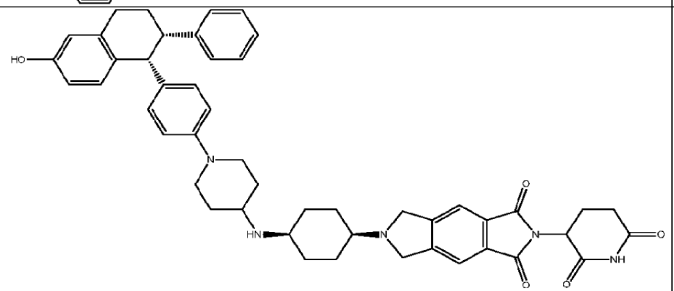
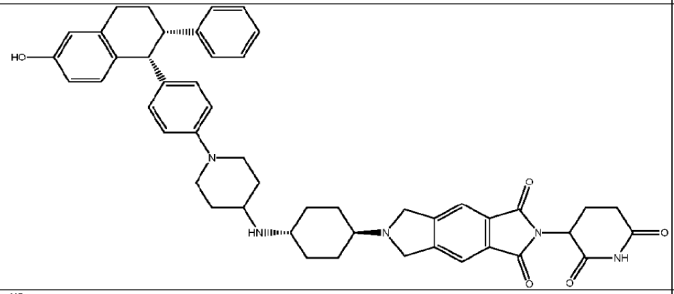
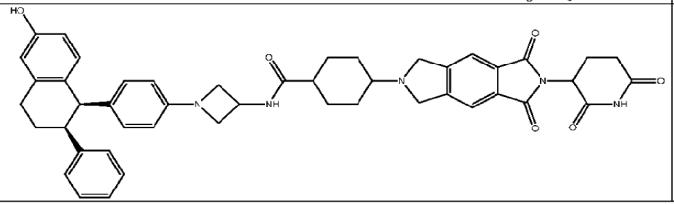
Compound No.	Chemical Structure	Chemical Name
B78		3-(6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B79		2-(2,6-dioxopiperidin-3-yl)-6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)piperidine-4-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B80		3-(6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)piperidine-4-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B81*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

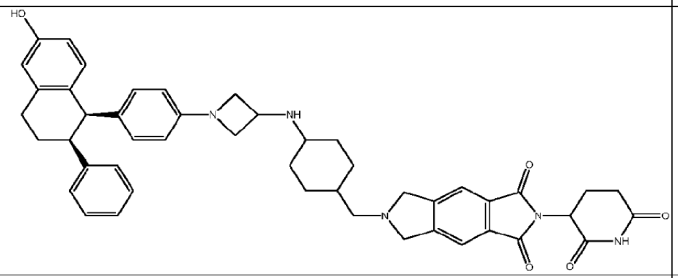
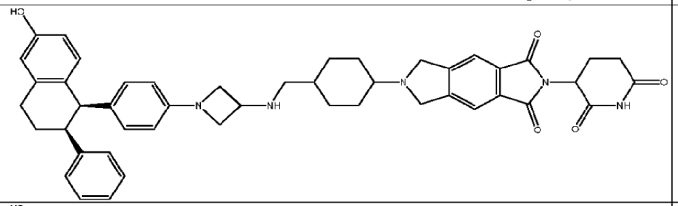
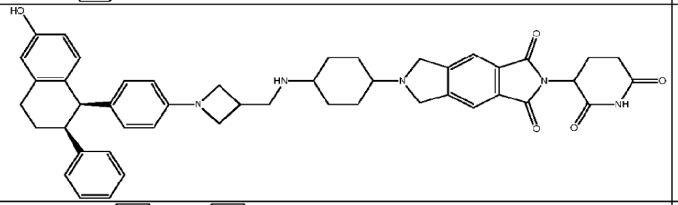
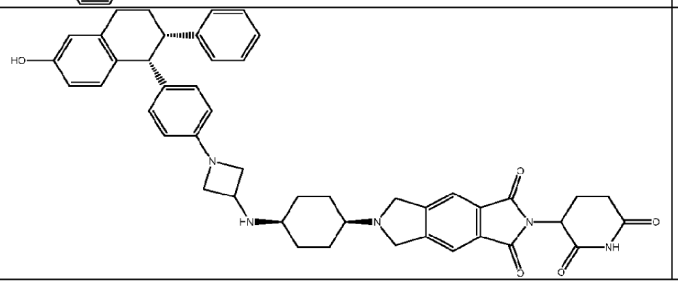
Compound No.	Chemical Structure	Chemical Name
B82*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B83		2-(2,6-dioxopiperidin-3-yl)-6-((4-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)cyclohexyl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B84		2-(2,6-dioxopiperidin-3-yl)-6-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)amino)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

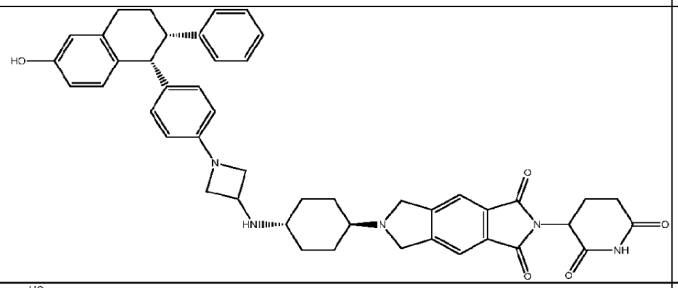
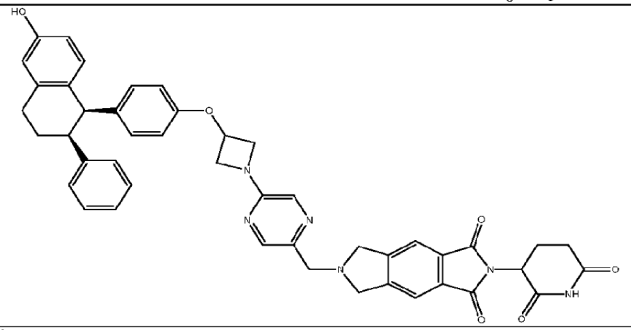
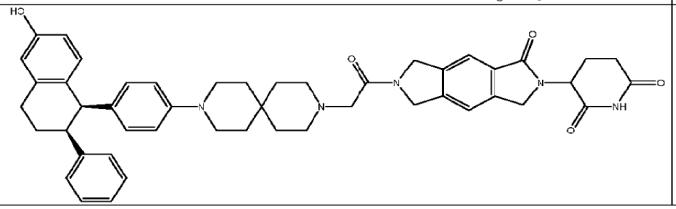
Compound No.	Chemical Structure	Chemical Name
B85*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrazin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B86*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(6-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-3-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B87*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(6-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridazin-3-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B88		2-(2,6-dioxopiperidin-3-yl)-6-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)(methyl)amino)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

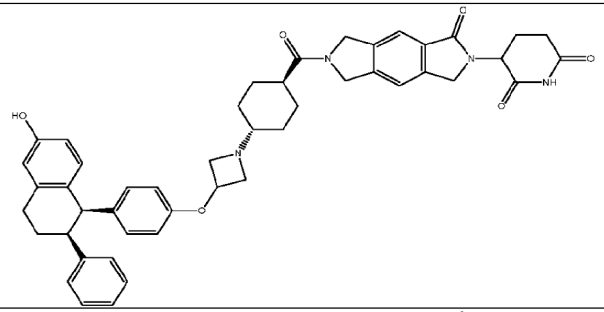
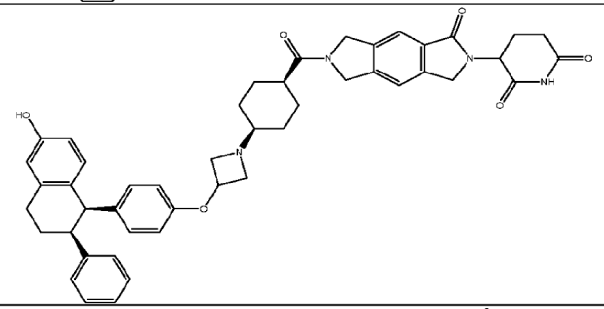
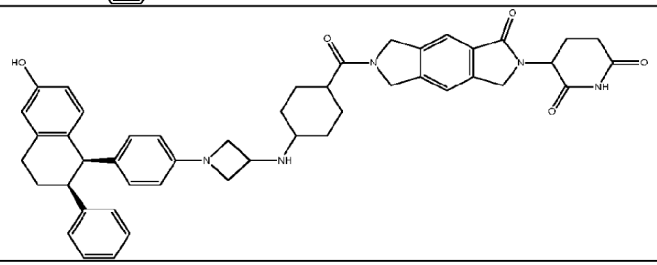
Compound No.	Chemical Structure	Chemical Name
B89		2-(2,6-dioxopiperidin-3-yl)-6-(5-((3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)methyl)pyrimidin-2-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B90		2-(2,6-dioxopiperidin-3-yl)-6-(5-((3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)methyl)pyridin-2-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B91		2-(2,6-dioxopiperidin-3-yl)-6-((6-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)pyridin-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

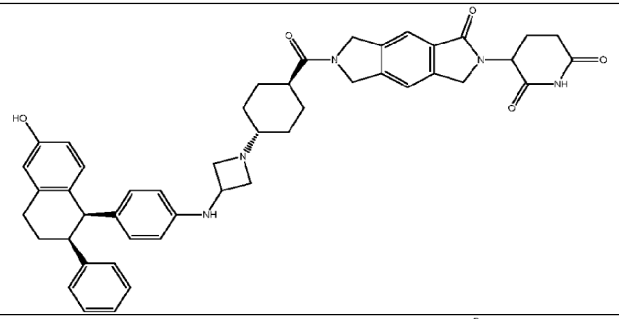
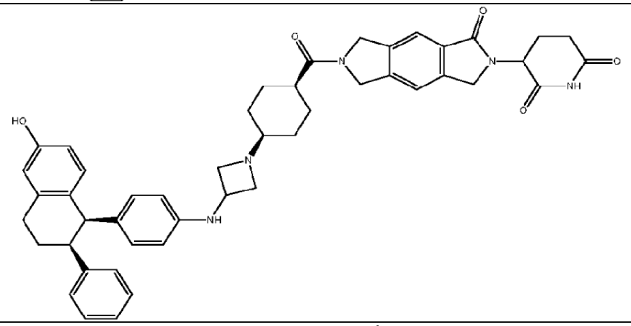
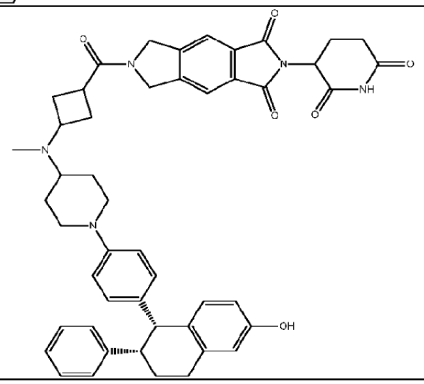
Compound No.	Chemical Structure	Chemical Name
B92		2-(2,6-dioxopiperidin-3-yl)-6-((2-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)pyrimidin-5-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B93		2-(6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)-N-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)acetamide
B94		3-(6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)-N-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)propenamide

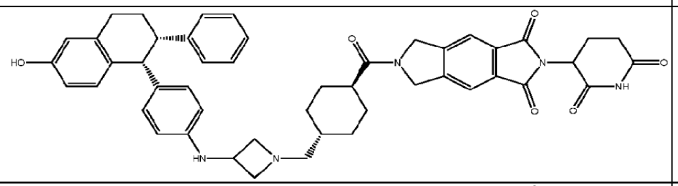
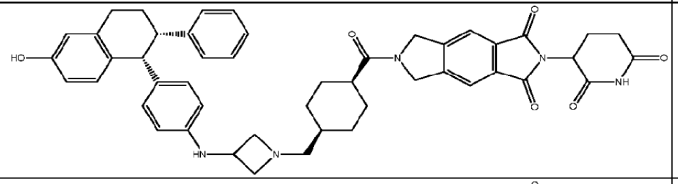
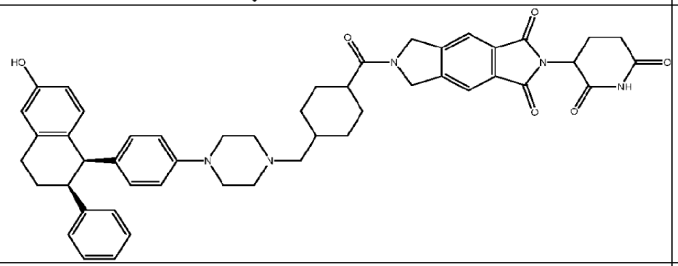
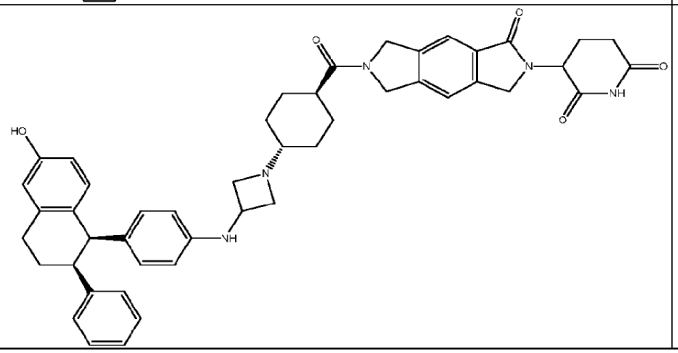
Compound No.	Chemical Structure	Chemical Name
B95		2-(2,6-dioxopiperidin-3-yl)-6-(4-(((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)(methyl)amino)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B96		2-(2,6-dioxopiperidin-3-yl)-6-((1S,4s)-4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)amino)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B97		2-(2,6-dioxopiperidin-3-yl)-6-((1R,4r)-4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)amino)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B98		4-(6-(2,6-dioxopiperidin-3-yl)-5,7-dioxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)-N-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)cyclohexane-1-carboxamide

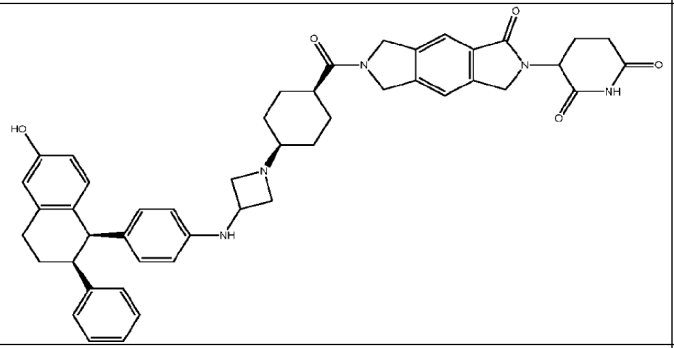
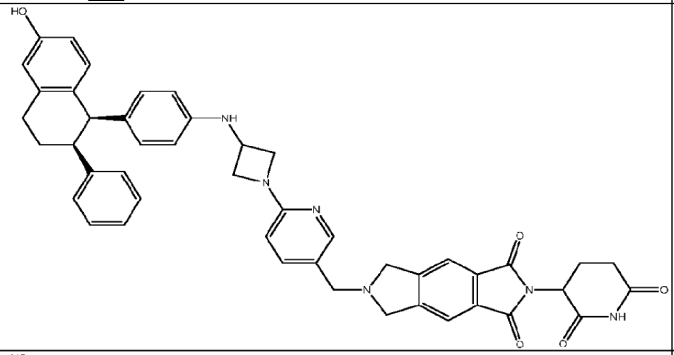
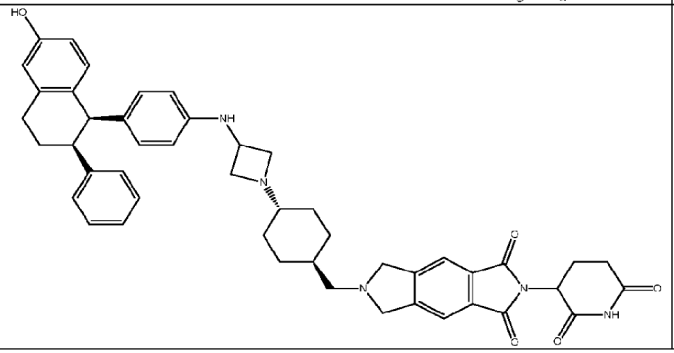
Compound No.	Chemical Structure	Chemical Name
B99		2-(2,6-dioxopiperidin-3-yl)-6-((4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)amino)cyclohexyl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B100		2-(2,6-dioxopiperidin-3-yl)-6-(4-(((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)amino)methyl)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B101		2-(2,6-dioxopiperidin-3-yl)-6-(4-(((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)methyl)amino)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B102		2-(2,6-dioxopiperidin-3-yl)-6-((1S,4s)-4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)amino)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

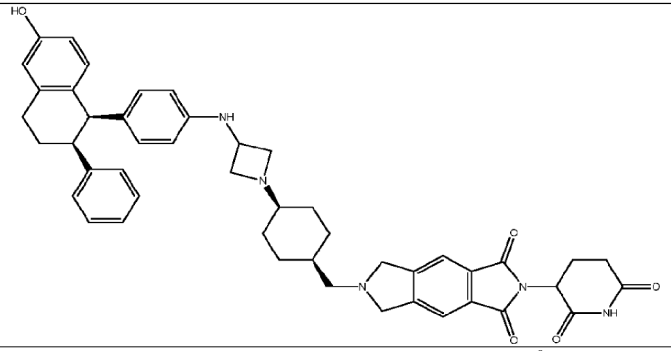
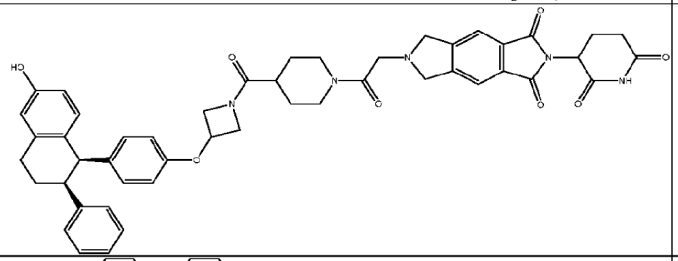
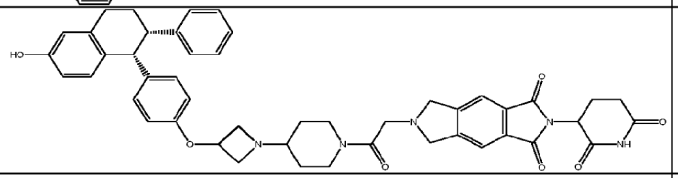
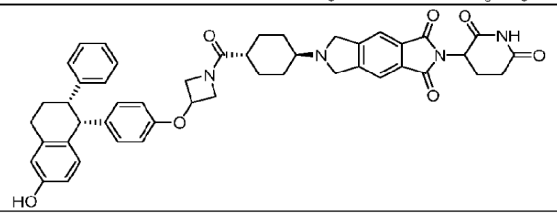
Compound No.	Chemical Structure	Chemical Name
B103		2-(2,6-dioxopiperidin-3-yl)-6-((1R,4r)-4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)amino)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B104		2-(2,6-dioxopiperidin-3-yl)-6-((5-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)pyrazin-2-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B105		3-(6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione

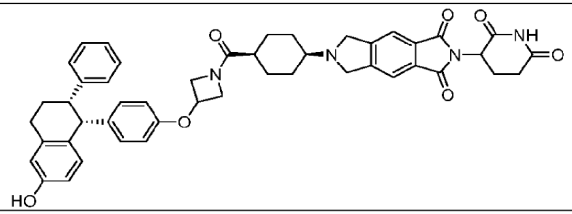
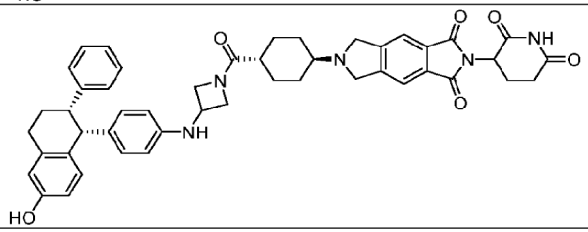
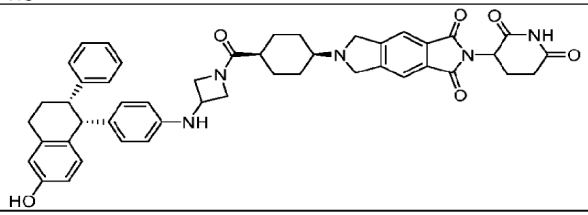
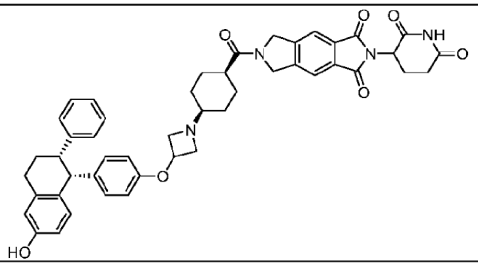
Compound No.	Chemical Structure	Chemical Name
B106		3-(6-((1R,4r)-4-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)cyclohexane-1-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B107		3-(6-((1S,4s)-4-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)cyclohexane-1-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B108		3-(6-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)amino)cyclohexane-1-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione

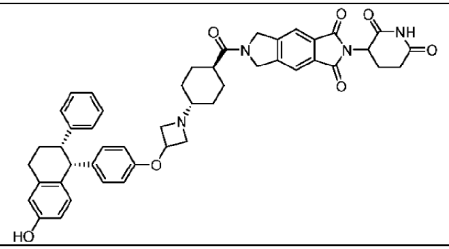
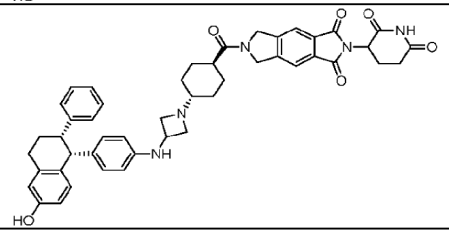
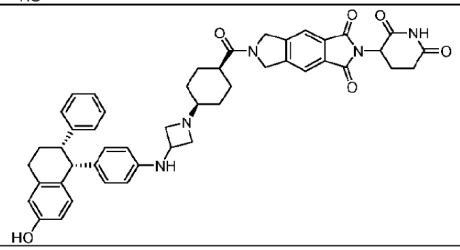
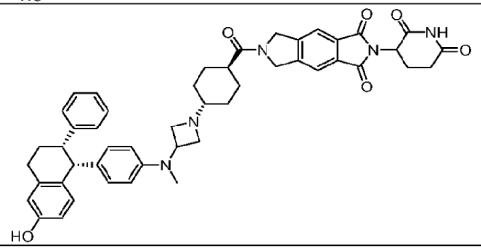
Compound No.	Chemical Structure	Chemical Name
B109		3-(6-((1R,4r)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)cyclohexane-1-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B110		3-(6-((1S,4s)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)cyclohexane-1-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B111		2-(2,6-dioxopiperidin-3-yl)-6-(3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)(methyl)amino)cyclobutane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

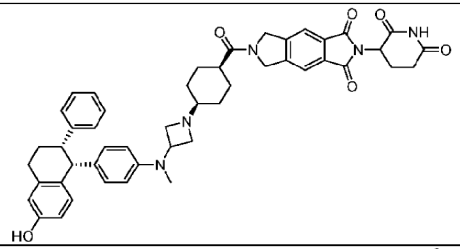
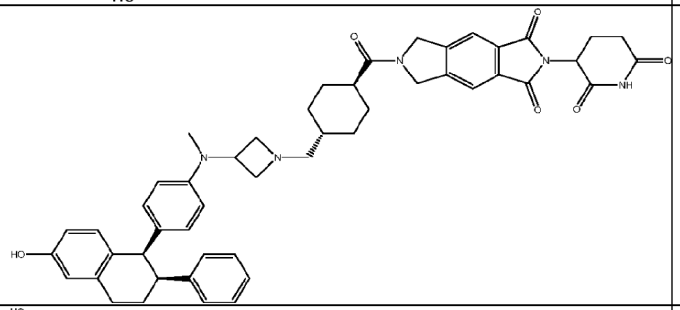
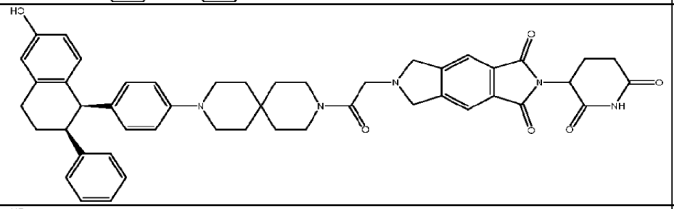
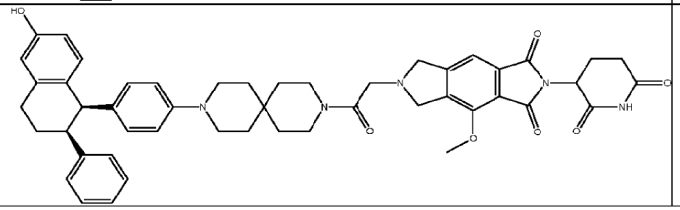
Compound No.	Chemical Structure	Chemical Name
B112		2-(2,6-dioxopiperidin-3-yl)-6-((1R,4r)-4-((3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)methyl)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B113		2-(2,6-dioxopiperidin-3-yl)-6-((1S,4s)-4-((3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)methyl)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B114		2-(2,6-dioxopiperidin-3-yl)-6-(4-((4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)methyl)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B115		3-(6-((1R,4r)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)cyclohexane-1-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione

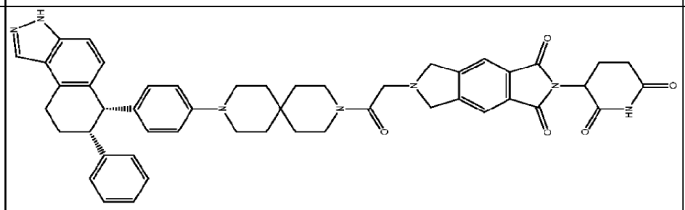
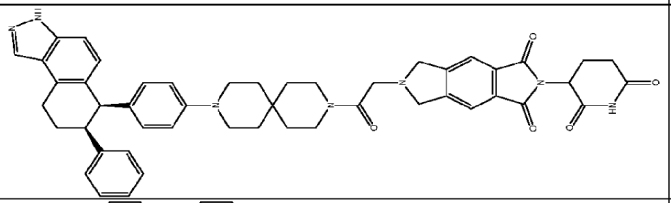
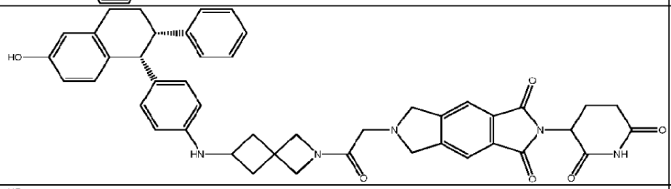
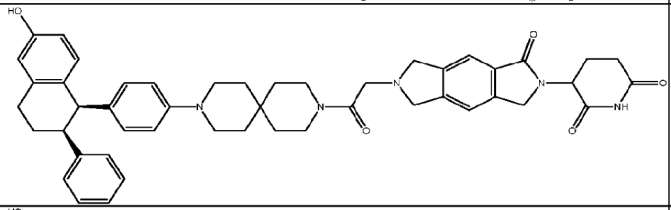
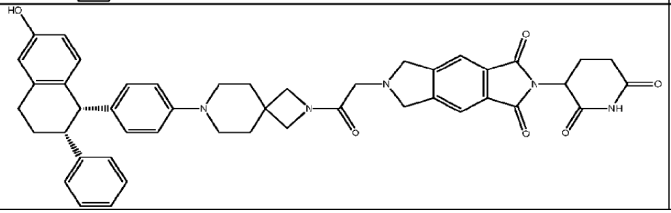
Compound No.	Chemical Structure	Chemical Name
B116		3-(6-((1S,4s)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)cyclohexane-1-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B117		2-(2,6-dioxopiperidin-3-yl)-6-((6-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)pyridin-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B118		2-(2,6-dioxopiperidin-3-yl)-6-(((1R,4r)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)cyclohexyl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

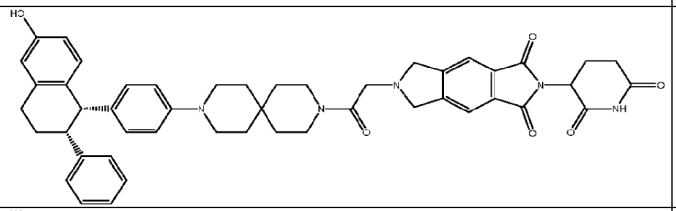
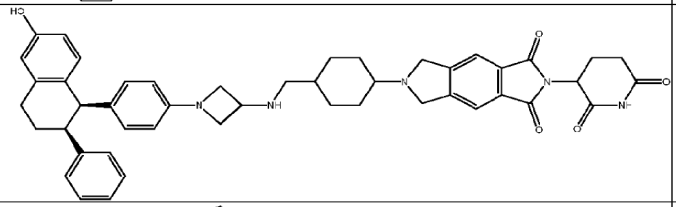
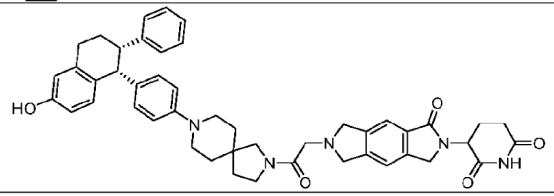
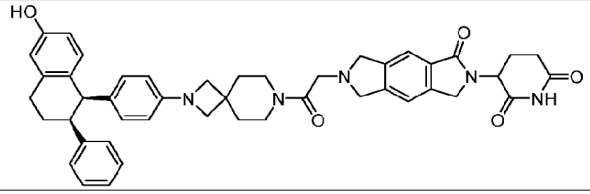
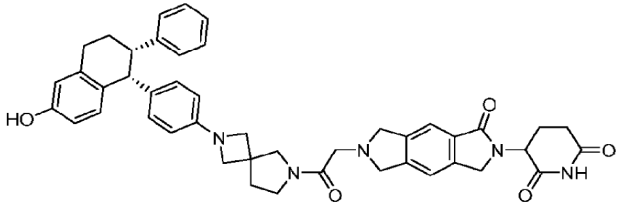
Compound No.	Chemical Structure	Chemical Name
B119		2-(2,6-dioxopiperidin-3-yl)-6-(((1S,4s)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)cyclohexyl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B120		2-(2,6-dioxopiperidin-3-yl)-6-(2-(4-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidine-1-carbonyl)piperidin-1-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B121		2-(2,6-dioxopiperidin-3-yl)-6-(2-(4-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)piperidin-1-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B122		2-(2,6-dioxopiperidin-3-yl)-6-((1S,4r)-4-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidine-1-carbonyl)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

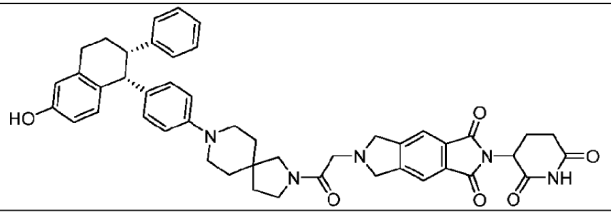
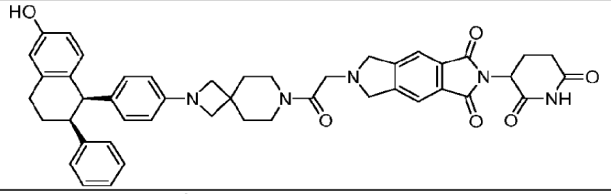
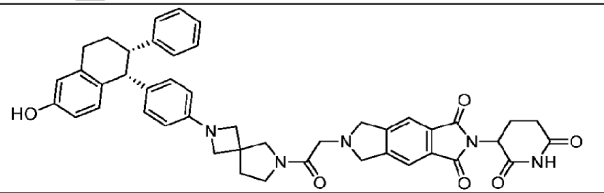
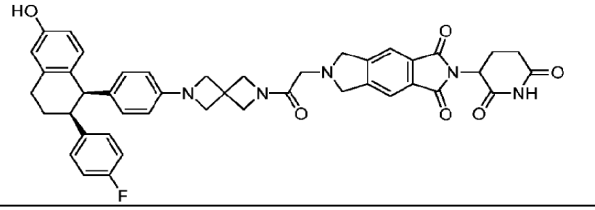
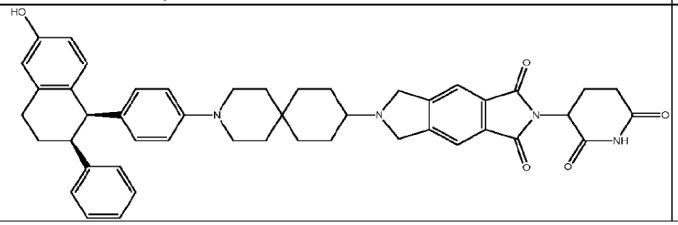
Compound No.	Chemical Structure	Chemical Name
B123		2-(2,6-dioxopiperidin-3-yl)-6-((1R,4s)-4-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidine-1-carbonyl)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B124		2-(2,6-dioxopiperidin-3-yl)-6-((1S,4r)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidine-1-carbonyl)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B125		2-(2,6-dioxopiperidin-3-yl)-6-((1R,4s)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidine-1-carbonyl)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B126		2-(2,6-dioxopiperidin-3-yl)-6-((1R,4s)-4-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

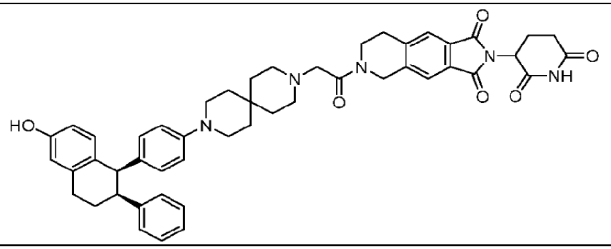
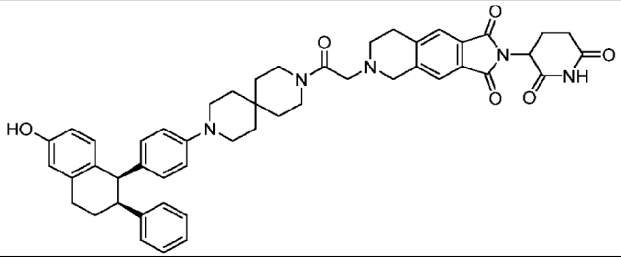
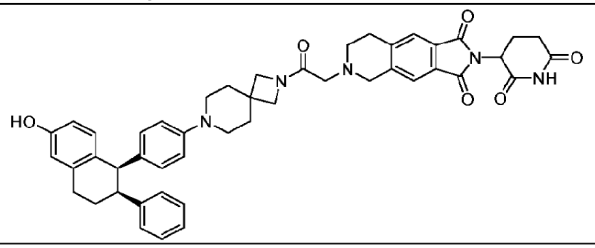
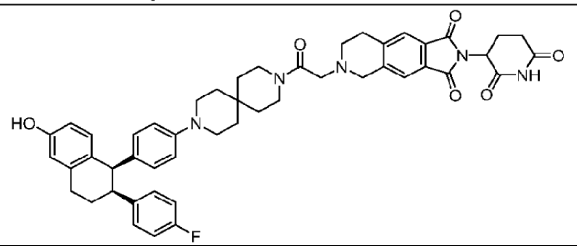
Compound No.	Chemical Structure	Chemical Name
B127		2-(2,6-dioxopiperidin-3-yl)-6-((1S,4r)-4-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B128		2-(2,6-dioxopiperidin-3-yl)-6-((1S,4r)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B129		2-(2,6-dioxopiperidin-3-yl)-6-((1R,4s)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)azetidin-1-yl)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B130		2-(2,6-dioxopiperidin-3-yl)-6-((1R,4r)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)(methyl)amino)azetidin-1-yl)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B131		2-(2,6-dioxopiperidin-3-yl)-6-((1S,4s)-4-(3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)(methyl)amino)azetidin-1-yl)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B132		2-(2,6-dioxopiperidin-3-yl)-6-((1R,4r)-4-((3-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)(methyl)amino)azetidin-1-yl)methyl)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B133		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B136		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-4-methoxy-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B138		2-(2,6-dioxopiperidin-3-yl)-6-(2-oxo-2-(9-(4-((6S,7R)-7-phenyl-6,7,8,9-tetrahydro-3H-benzo[e]indazol-6-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B139		2-(2,6-dioxopiperidin-3-yl)-6-(2-oxo-2-(9-(4-((6R,7S)-7-phenyl-6,7,8,9-tetrahydro-3H-benzo[e]indazol-6-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B163		2-(2,6-dioxopiperidin-3-yl)-6-(2-(6-((4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)amino)-2-azaspiro[3.3]heptan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B166		3-(6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B179		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B180		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B181		2-(2,6-dioxopiperidin-3-yl)-6-(4-(((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidin-3-yl)amino)methyl)cyclohexyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B182*		3-(6-(2-(8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,8-diazaspiro[4.5]decan-2-yl)-2-oxoethyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B183*		3-(6-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)-2-oxoethyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B184*		3-(6-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.4]octan-6-yl)-2-oxoethyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B185*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,8-diazaspiro[4.5]decan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B186*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B187*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.4]octan-6-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B188*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(6-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,6-diazaspiro[3.3]heptan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B189		2-(2,6-dioxopiperidin-3-yl)-6-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-azaspiro[5.5]undecan-9-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B190*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-5,6,7,8-tetrahydro-1H-pyrrolo[3,4-g]isoquinoline-1,3(2H)-dione
B191*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-5,6,7,8-tetrahydro-1H-pyrrolo[3,4-g]isoquinoline-1,3(2H)-dione
B192*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-5,6,7,8-tetrahydro-1H-pyrrolo[3,4-g]isoquinoline-1,3(2H)-dione
B193*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-5,6,7,8-tetrahydro-1H-pyrrolo[3,4-g]isoquinoline-1,3(2H)-dione

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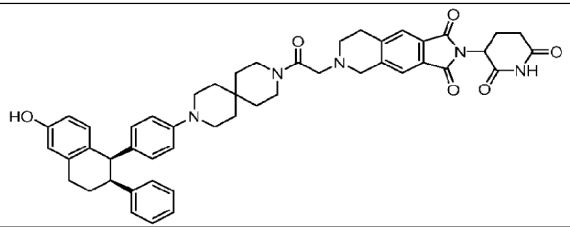
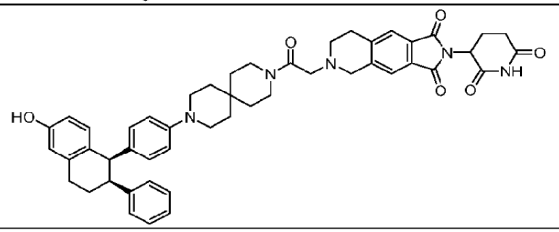
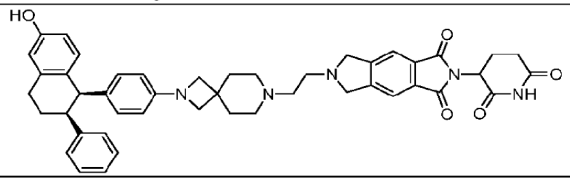
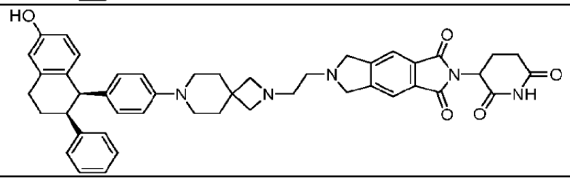
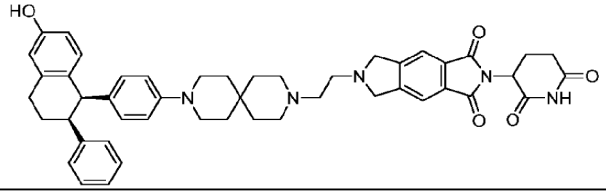
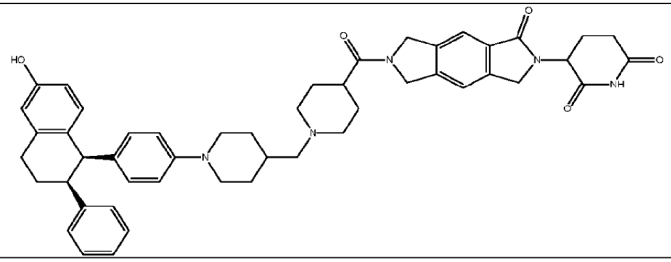
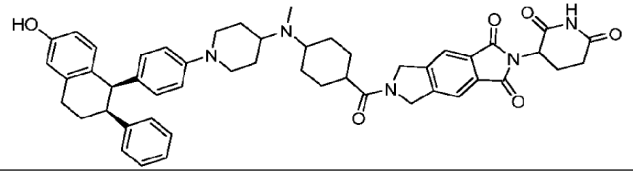
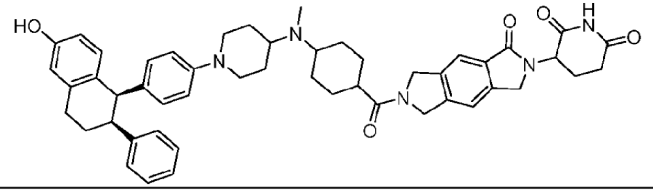
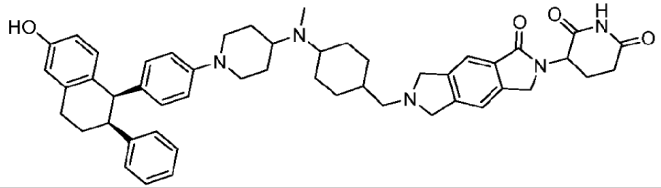
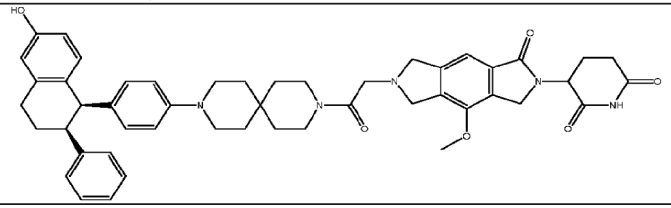
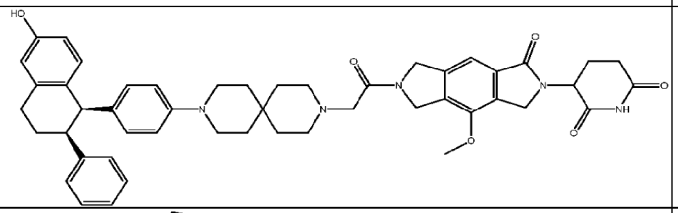
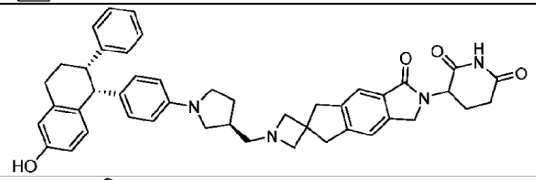
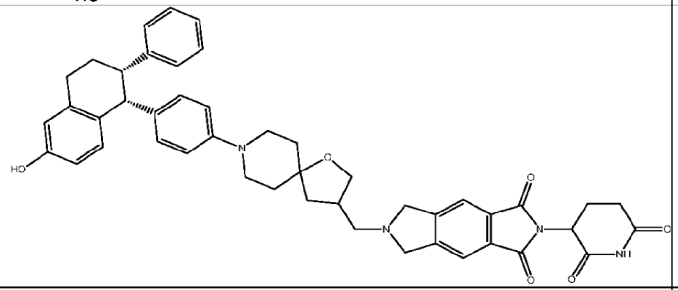
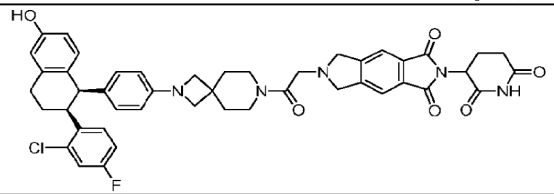
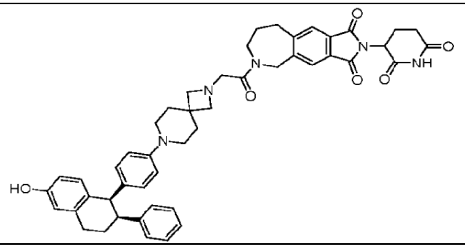
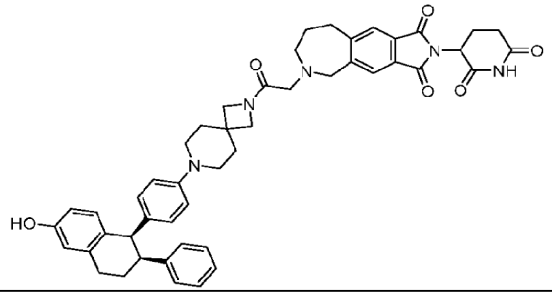
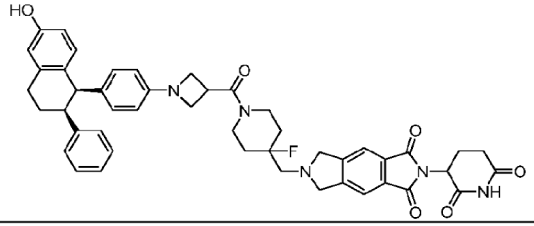
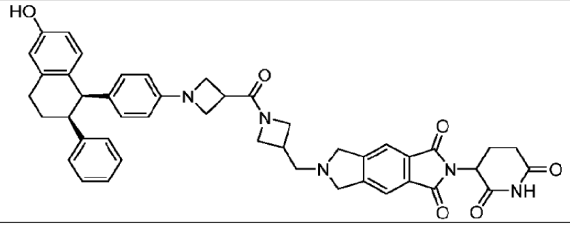
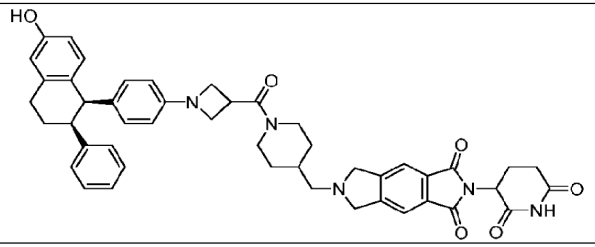
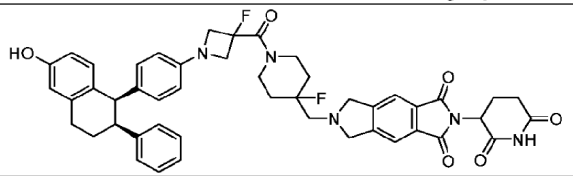
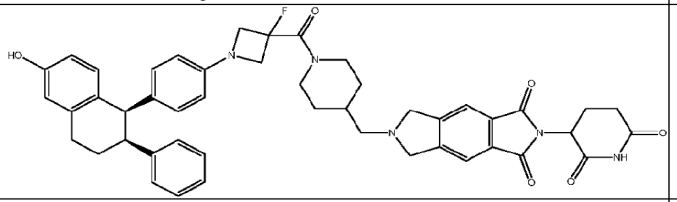
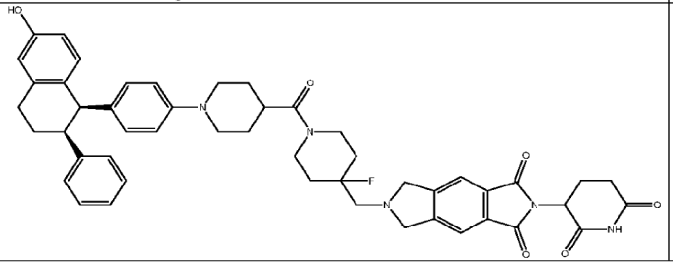
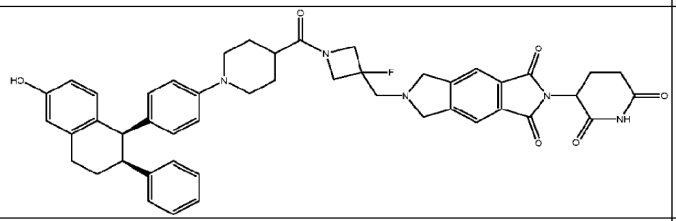
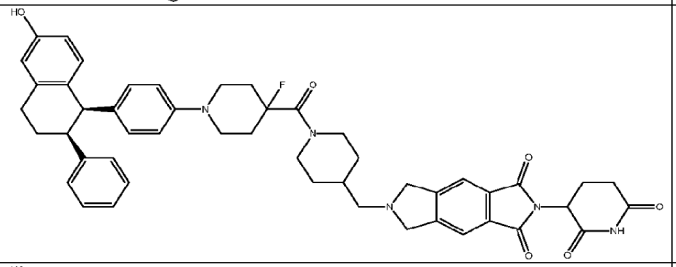
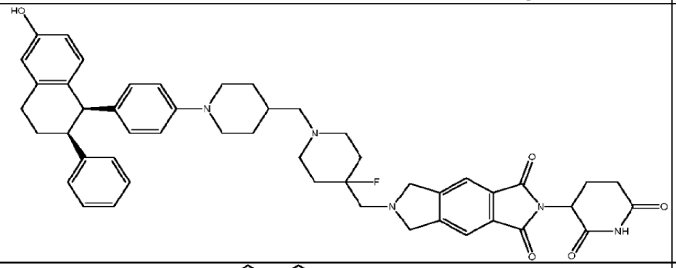
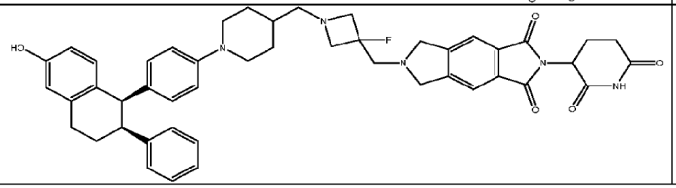
Compound No.	Chemical Structure	Chemical Name
B194*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-5,6,7,8-tetrahydro-1H-pyrrolo[3,4-g]isoquinoline-1,3(2H)-dione
B195*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-5,6,7,8-tetrahydro-1H-pyrrolo[3,4-g]isoquinoline-1,3(2H)-dione
B196*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)ethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B197*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)ethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B198*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

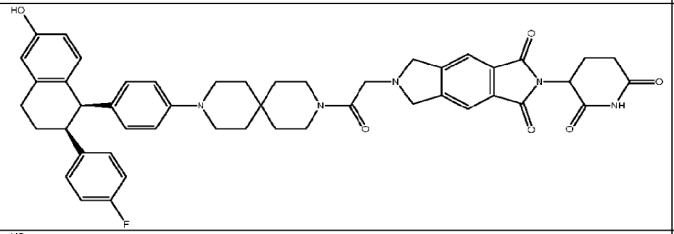
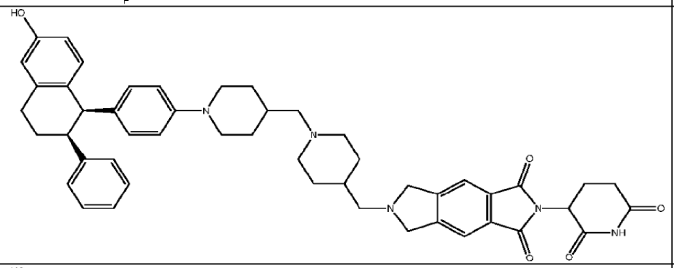
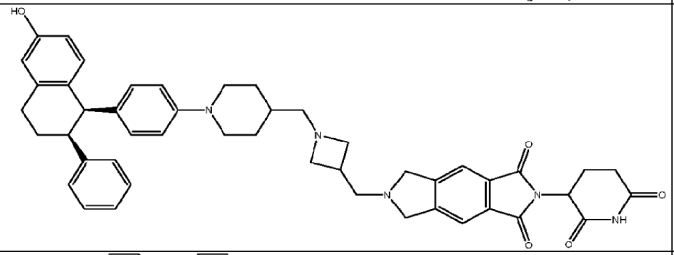
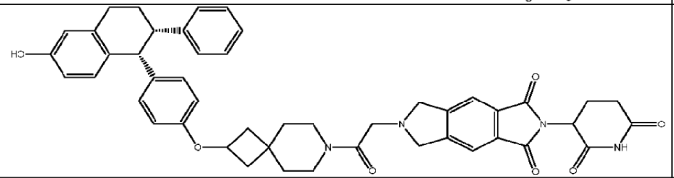
Compound No.	Chemical Structure	Chemical Name
B199		3-(6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidine-4-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B200		2-(2,6-dioxopiperidin-3-yl)-6-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)(methyl)amino)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B201		3-(6-(4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)(methyl)amino)cyclohexane-1-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B202		3-(6-((4-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)(methyl)amino)cyclohexyl)methyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B203		3-(6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-4-methoxy-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B210		3-(6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-4-methoxy-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B217		3-(1-(((S)-1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)pyrrolidin-3-yl)methyl)-1'-oxo-5',7'-dihydro-1'H-spiro[azetidine-3,6'-cyclopenta[f]isoindol]-2'(3'H)-yl)piperidine-2,6-dione
B235		2-(2,6-dioxopiperidin-3-yl)-6-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B259*		6-(2-(2-(4-((1R,2S)-2-(2-chloro-4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)-2-oxoethyl)-2-(2,6-dioxopiperidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B260*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-6,7,8,9-tetrahydroazepino[3,4-f]isoindole-1,3(2H,5H)-dione
B261*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7,8,9-tetrahydroazepino[3,4-f]isoindole-1,3(2H,5H)-dione
B262		2-(2,6-dioxopiperidin-3-yl)-6-((4-fluoro-1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidine-3-carbonyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B263		2-(2,6-dioxopiperidin-3-yl)-6-((1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidine-3-carbonyl)azetidin-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B264		2-(2,6-dioxopiperidin-3-yl)-6-((1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidine-3-carbonyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B265		2-(2,6-dioxopiperidin-3-yl)-6-((4-fluoro-1-(3-fluoro-1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidine-3-carbonyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B266		2-(2,6-dioxopiperidin-3-yl)-6-((1-(3-fluoro-1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidine-3-carbonyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B267		2-(2,6-dioxopiperidin-3-yl)-6-((4-fluoro-1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine-4-carbonyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B268		2-(2,6-dioxopiperidin-3-yl)-6-((3-fluoro-1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine-4-carbonyl)azetidin-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B269		2-(2,6-dioxopiperidin-3-yl)-6-((1-(4-fluoro-1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine-4-carbonyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B270		2-(2,6-dioxopiperidin-3-yl)-6-((4-fluoro-1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B271		2-(2,6-dioxopiperidin-3-yl)-6-((3-fluoro-1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B272		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-2-(4-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B273		2-(2,6-dioxopiperidin-3-yl)-6-((1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B274		2-(2,6-dioxopiperidin-3-yl)-6-((1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B275		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

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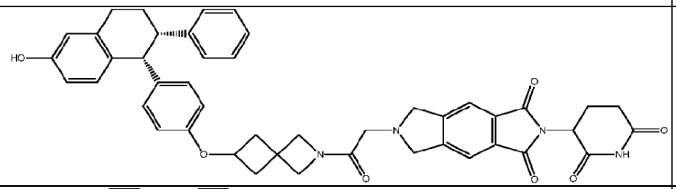
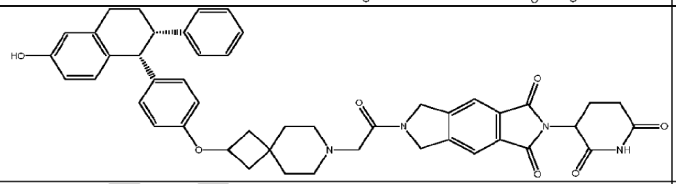
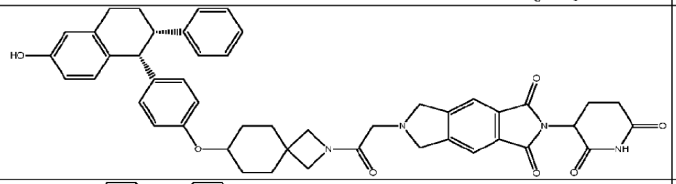
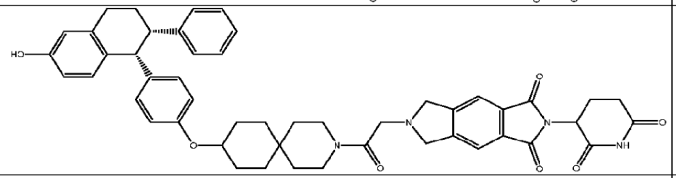
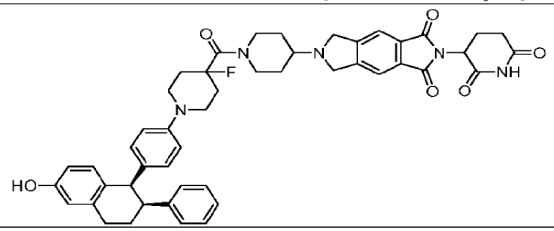
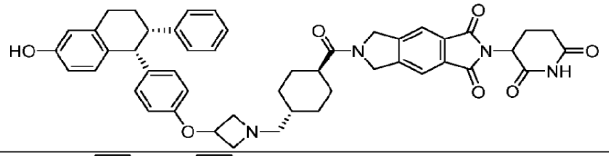
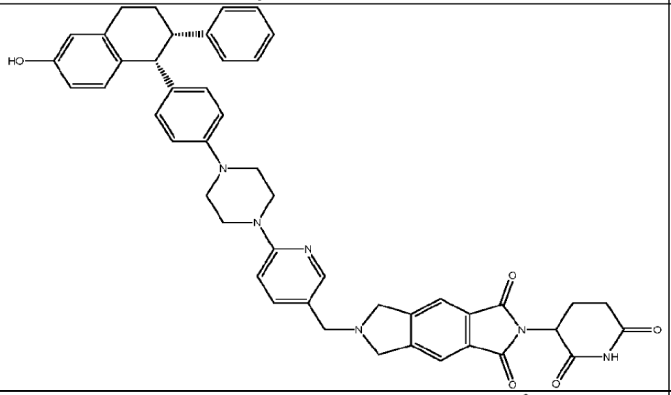
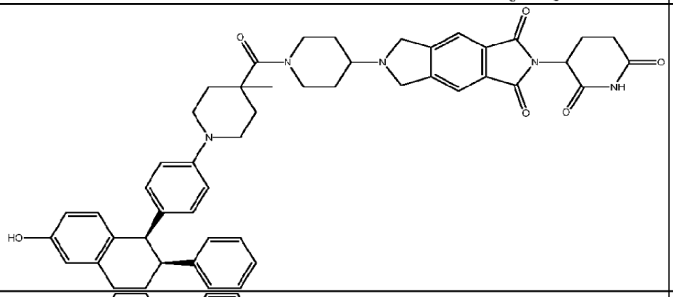
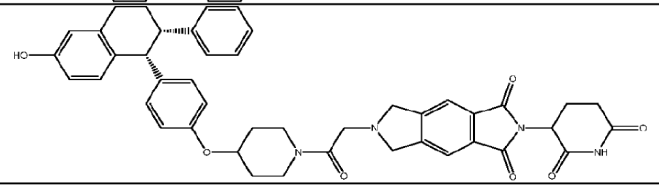
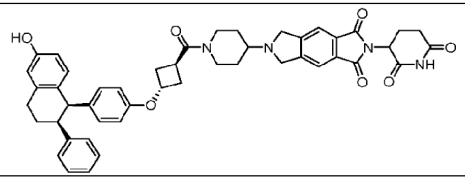
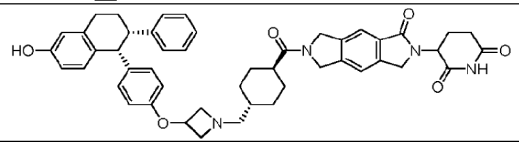
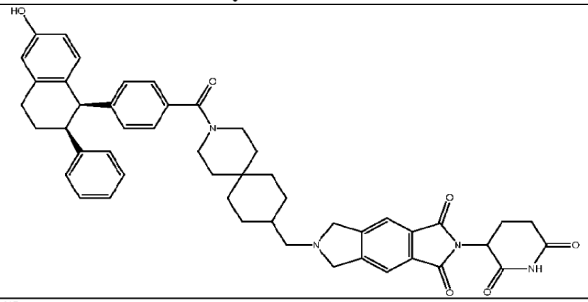
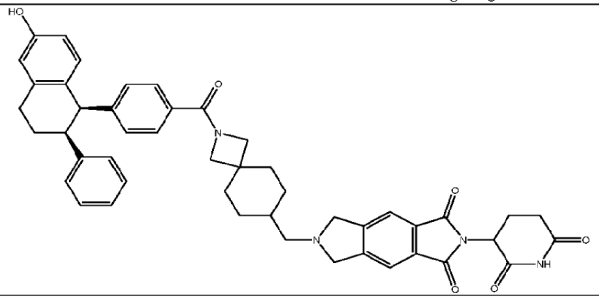
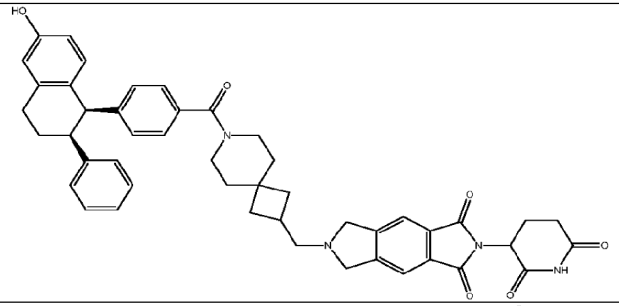
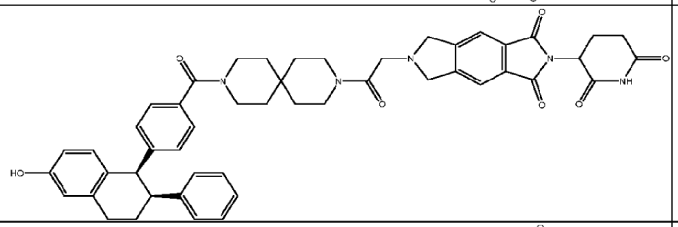
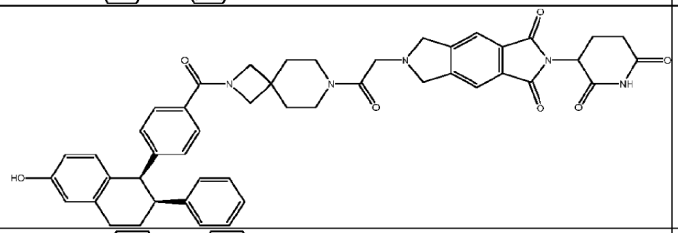
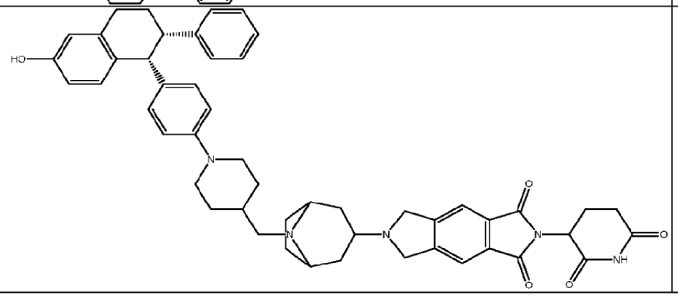
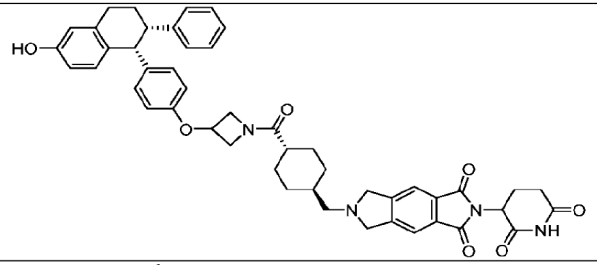
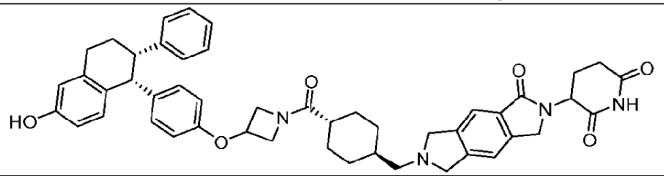
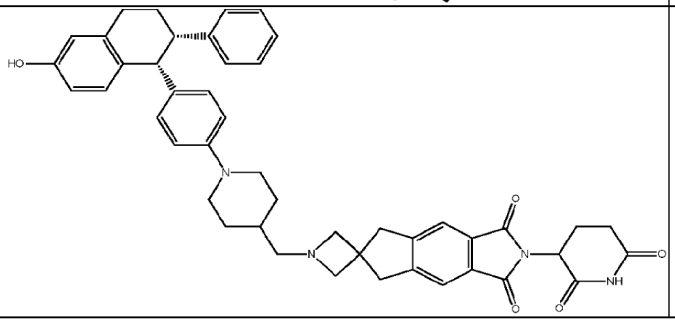
Compound No.	Chemical Structure	Chemical Name
B276		2-(2,6-dioxopiperidin-3-yl)-6-(2-(6-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)-2-azaspiro[3.3]heptan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B277		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B278		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)-2-azaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B279		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)-3-azaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B280		2-(2,6-dioxopiperidin-3-yl)-6-(1-(4-fluoro-1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine-4-carbonyl)piperidin-4-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B281		2-(2,6-dioxopiperidin-3-yl)-6-((1R,4r)-4-((3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)methyl)cyclohexane-1-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B282		2-(2,6-dioxopiperidin-3-yl)-6-((6-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperazin-1-yl)pyridin-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B283		2-(2,6-dioxopiperidin-3-yl)-6-(1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-4-methylpiperidine-4-carbonyl)piperidin-4-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B284		2-(2,6-dioxopiperidin-3-yl)-6-(2-(4-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)piperidin-1-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B285		2-(2,6-dioxopiperidin-3-yl)-6-(1-((1R,3r)-3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)cyclobutane-1-carbonyl)piperidin-4-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B286		3-(6-((1R,4r)-4-((3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)methyl)cyclohexane-1-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B287		2-(2,6-dioxopiperidin-3-yl)-6-((3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzoyl)-3-azaspiro[5.5]undecan-9-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B288		2-(2,6-dioxopiperidin-3-yl)-6-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzoyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B289		2-(2,6-dioxopiperidin-3-yl)-6-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzoyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B290		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B291		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)benzoyl)-2,7-diazaspiro[3.5]nonan-7-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B292		2-(2,6-dioxopiperidin-3-yl)-6-(8-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-8-azabicyclo[3.2.1]octan-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B293		2-(2,6-dioxopiperidin-3-yl)-6-(((1R,4r)-4-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidine-1-carbonyl)cyclohexyl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B294		3-(6-(((1R,4r)-4-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidine-1-carbonyl)cyclohexyl)methyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B296		2'-(2,6-dioxopiperidin-3-yl)-1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-5',7'-dihydro-1'H-spiro[azetidine-3,6'-cyclopenta[f]isoindole]-1',3'(2'H)-dione

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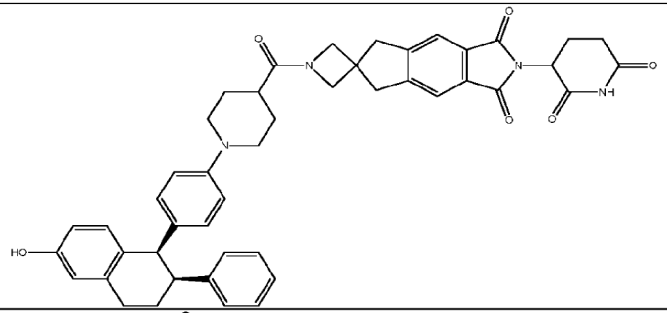
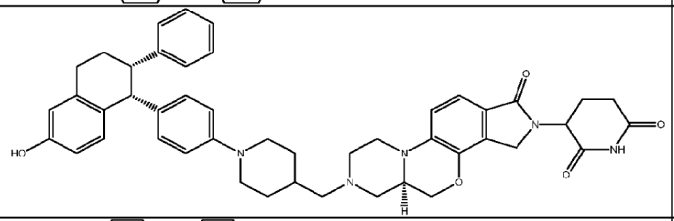
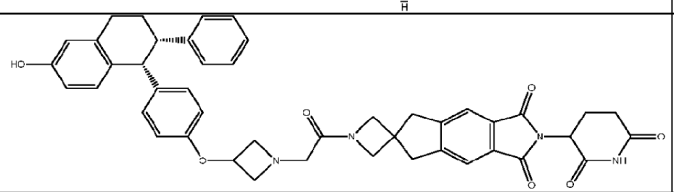
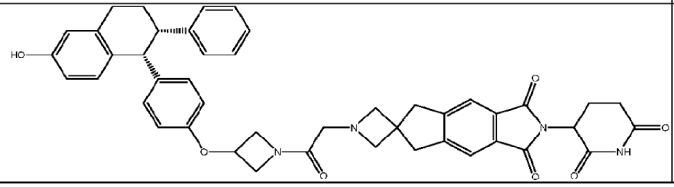
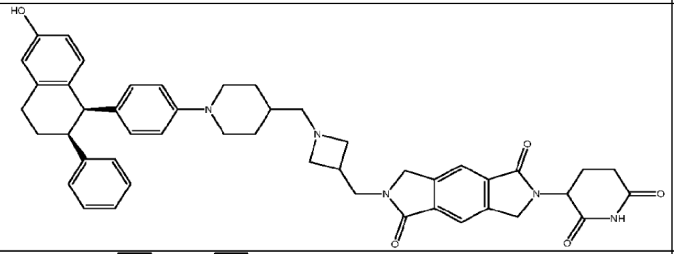
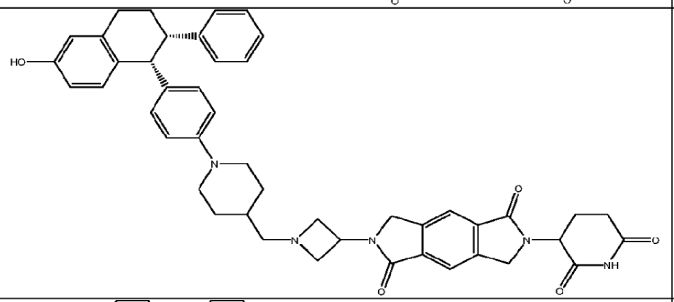
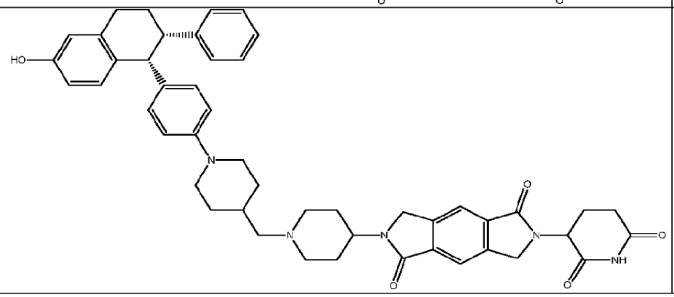
Compound No.	Chemical Structure	Chemical Name
B297		2'-(2,6-dioxopiperidin-3-yl)-1-(1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine-4-carbonyl)-5',7'-dihydro-1'H-spiro[azetidine-3,6'-cyclopenta[f]isoindole]-1',3'(2'H)-dione
B298		3-((R)-7-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B299		2'-(2,6-dioxopiperidin-3-yl)-1-(2-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)acetyl)-5',7'-dihydro-1'H-spiro[azetidine-3,6'-cyclopenta[f]isoindole]-1',3'(2'H)-dione
B300		2'-(2,6-dioxopiperidin-3-yl)-1-(2-(3-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenoxy)azetidin-1-yl)-2-oxoethyl)-5',7'-dihydro-1'H-spiro[azetidine-3,6'-cyclopenta[f]isoindole]-1',3'(2'H)-dione

Compound No.	Chemical Structure	Chemical Name
B301		2-(2,6-dioxopiperidin-3-yl)-6-((1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)methyl)-2,3,6,7-tetrahydropyrrolo[3,4-f]isoindole-1,5-dione
B302		2-(2,6-dioxopiperidin-3-yl)-6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)-2,3,6,7-tetrahydropyrrolo[3,4-f]isoindole-1,5-dione
B303		2-(2,6-dioxopiperidin-3-yl)-6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-2,3,6,7-tetrahydropyrrolo[3,4-f]isoindole-1,5-dione

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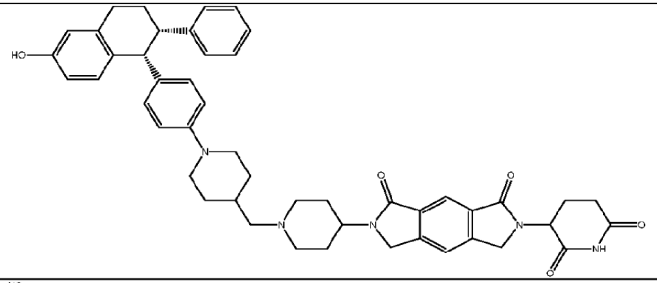
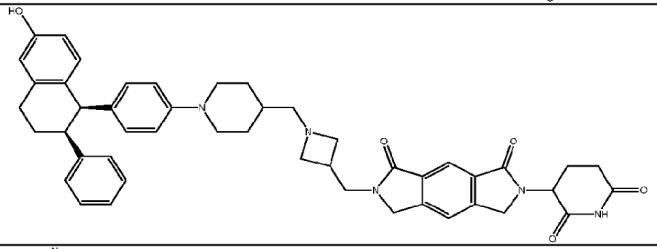
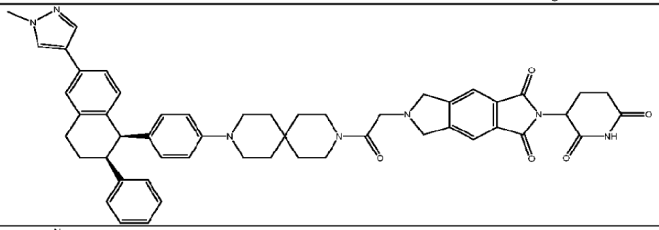
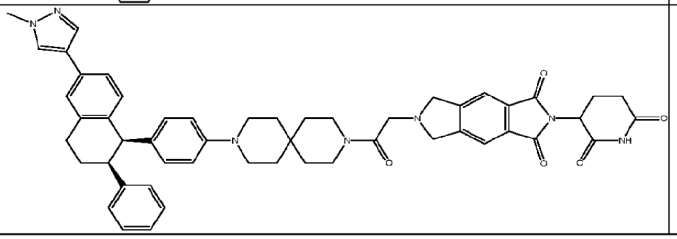
Compound No.	Chemical Structure	Chemical Name
B304		2-(2,6-dioxopiperidin-3-yl)-6-(1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)-2,3,5,6-tetrahydropyrrolo[3,4-f]isoindole-1,7-dione
B305		2-(2,6-dioxopiperidin-3-yl)-6-((1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)azetidin-3-yl)methyl)-2,3,5,6-tetrahydropyrrolo[3,4-f]isoindole-1,7-dione
B323		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-(1-methyl-1H-pyrazol-4-yl)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B323		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-(1-methyl-1H-pyrazol-4-yl)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

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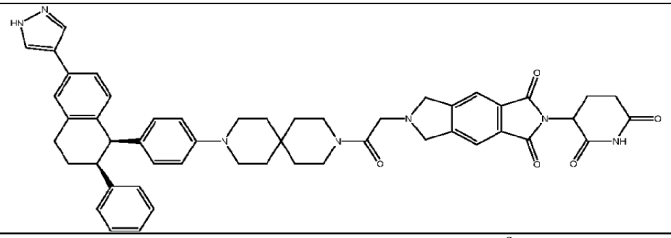
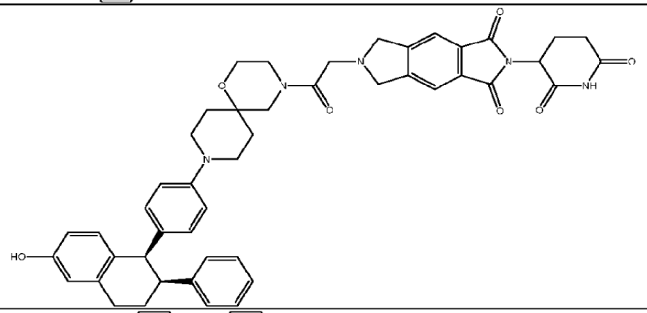
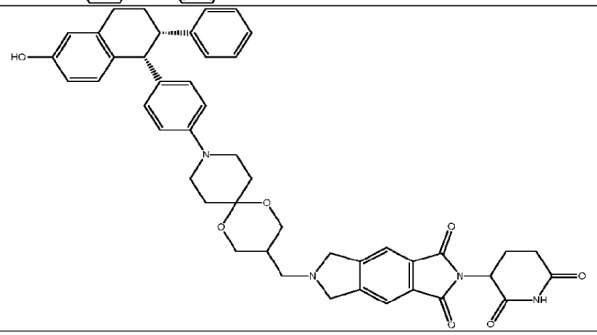
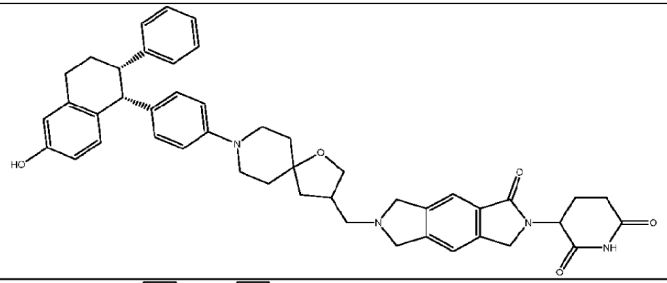
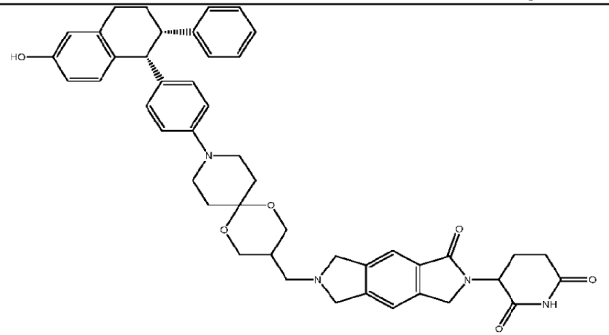
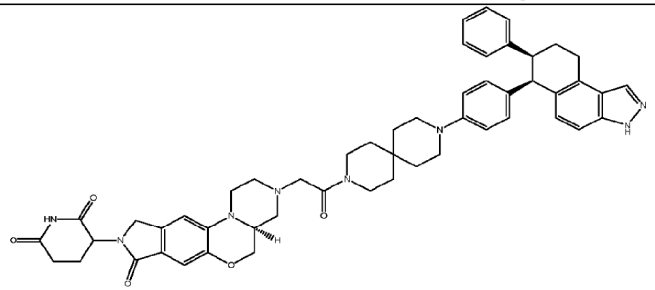
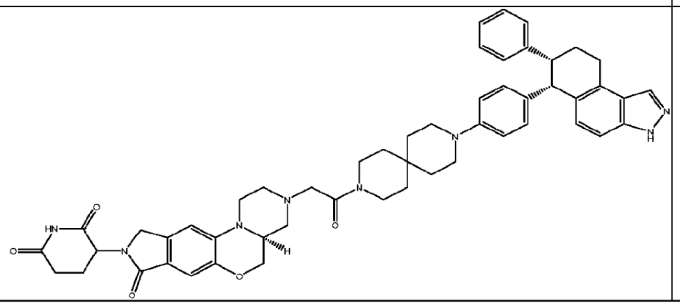
Compound No.	Chemical Structure	Chemical Name
B324		2-(2,6-dioxopiperidin-3-yl)-6-(2-oxo-2-(9-(4-((1R,2S)-2-phenyl-6-(1H-pyrazol-4-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B325		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
B338		2-(2,6-dioxopiperidin-3-yl)-6-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

Compound No.	Chemical Structure	Chemical Name
B352		3-(6-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B355		3-(6-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
B389		3-((S)-8-oxo-3-(2-oxo-2-(9-(4-((6R,7S)-7-phenyl-6,7,8,9-tetrahydro-3H-benzo[e]indazol-6-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

Compound No.	Chemical Structure	Chemical Name
B390		3-((S)-8-oxo-3-(2-oxo-2-(9-(4-((6S,7R)-7-phenyl-6,7,8,9-tetrahydro-3H-benzo[e]indazol-6-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

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[0202] The compounds of the present disclosure may possess advantageous characteristics, as compared to known compounds, such as known estrogen receptor degraders. For example, the compounds of the present disclosure may display more potent estrogen receptor activity, more favorable pharmacokinetic properties (*e.g.*, as measured by C_{max}, T_{max}, and/or AUC), and/or less interaction with other cellular targets (*e.g.*, hepatic cellular transporter such as OATP1B1) and accordingly improved safety (*e.g.*, drug-drug interaction). These beneficial properties of the compounds of the present disclosure can be measured according to methods commonly available in the art, such as methods exemplified herein.

[0203] Due to the existence of double bonds, the compounds of the present disclosure may be in *cis* or *trans*, or Z or E, configuration. It is understood that although one configuration may be depicted in the structure of the compounds or formulae of the present disclosure, the present disclosure also encompasses the other configuration. For example, the compounds or formulae of the present disclosure may be depicted in *cis* or *trans*, or Z or E, configuration.

[0204] In certain embodiments, a compound of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a pharmaceutically acceptable salt. In certain embodiments, a compound of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a solvate. In certain embodiments, a compound of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a hydrate.

Pharmaceutically acceptable salts

[0205] In certain embodiments, the compounds disclosed herein exist as their pharmaceutically acceptable salts. In certain embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In certain embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[0206] In certain embodiments, the compounds described herein possess acidic or basic groups and therefor react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In certain embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or by

separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[0207] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid, or inorganic base, such salts including acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-napthalenesulfonate, 2-napthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylateundeconate, and xylenesulfonate.

[0208] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-

phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

[0209] In certain embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, or sulfate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4}$ alkyl$)_4$, and the like.

[0210] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In certain embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Solvates

[0211] "Solvate" refers to forms of the compound that are associated with a solvent or water (also referred to as "hydrate"), usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The compounds of the disclosure may be prepared *e.g.,* in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[0212] Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates are within the scope of the disclosure.

[0213] It will also be appreciated by those skilled in organic chemistry that many organic compounds can exist in more than one crystalline form. For example, crystalline form may vary

from solvate to solvate. Thus, all crystalline forms or the pharmaceutically acceptable solvates thereof are contemplated and are within the scope of the present disclosure.

[0214] In certain embodiments, the compounds described herein exist as solvates. The present disclosure provides for methods of treating diseases by administering such solvates. The present disclosure further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[0215] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Isomers (stereoisomers, geometric isomer, tautomer, etc.)

[0216] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers."

[0217] Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers." When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R - and S - sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+)- or (-)- isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is termed a "racemic mixture".

[0218] As used herein a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (*i.e.,* in enantiomeric excess). In other words, an "S" form of the compound is substantially free from the "R" form of the compound and is, thus, in enantiomeric excess of the "R" form. The term "enantiomerically pure" or "pure enantiomer" denotes that the

compound comprises more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

[0219] As used herein and unless otherwise indicated, the term "enantiomerically pure (R)-compound" refers to at least about 95% by weight (R)-compound and at most about 5% by weight (S)-compound, at least about 99% by weight (R)-compound and at most about 1% by weight (S)-compound, or at least about 99.9 % by weight (R)-compound and at most about 0.1% by weight (S)-compound. In certain embodiments, the weights are based upon total weight of compound.

[0220] As used herein and unless otherwise indicated, the term "enantiomerically pure (S)-compound" refers to at least about 95% by weight (S)-compound and at most about 5% by weight (R)-compound, at least about 99% by weight (S)-compound and at most about 1% by weight (R)-compound or at least about 99.9% by weight (S)-compound and at most about 0.1% by weight (R)-compound. In certain embodiments, the weights are based upon total weight of compound.

[0221] In the compositions provided herein, an enantiomerically pure compound or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising enantiomerically pure (R)-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure (R)-compound. In certain embodiments, the enantiomerically pure (R)-compound in such compositions can, for example, comprise, at least about 95% by weight (R)-compound and at most about 5% by weight (S)-compound, by total weight of the compound. For example, a pharmaceutical composition comprising enantiomerically pure (S)-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure (S)-compound. In certain embodiments, the enantiomerically pure (S)-compound in such compositions can, for example, comprise, at least about 95% by weight (S)-compound and at most about 5% by weight (R)-compound, by total weight of the compound. In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

[0222] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic

or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

[0223] In certain embodiments, the compounds described herein exist as geometric isomers. In certain embodiments, the compounds described herein possess one or more double bonds. The compounds disclosed herein include all *cis*, *trans*, *syn*, *anti*, *entgegen* (E), and *zusammen* (Z) isomers as well as the corresponding mixtures thereof. All geometric forms of the compounds disclosed herein are contemplated and are within the scope of the disclosure.

[0224] In certain embodiments, the compounds disclosed herein possess one or more chiral centers and each center exists in the R configuration or S configuration. The compounds disclosed herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. All diastereomeric, enantiomeric, and epimeric forms of the compounds disclosed herein are contemplated and are within the scope of the disclosure.

[0225] In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In certain embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In certain embodiments, dissociable complexes are preferred. In certain embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In certain embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In certain embodiments, the optically pure enantiomer is then recovered, along with the resolving agent.

Tautomers

[0226] In certain embodiments, compounds described herein exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein.

[0227] Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and an adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either

acid or base. Another example of tautomerism is the aci- and nitro-forms of phenylnitromethane, that are likewise formed by treatment with acid or base. Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest. All tautomeric forms of the compounds disclosed herein are contemplated and are within the scope of the disclosure. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Pharmaceutical Compositions

[0228] In certain embodiments, the compound described herein is administered as a pure chemical. In some embodiments, the compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[0229] Accordingly, the present disclosure provides pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[0230] In certain embodiments, the compound provided herein is substantially pure, in that it contains less than about 5%, less than about 1%, or less than about 0.1% of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method.

[0231] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.,* an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using

experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[0232] In some embodiments, the pharmaceutical composition is formulated for oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, intrapulmonary, intradermal, intrathecal and epidural and intranasal administration. Parenteral administration includes intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. In some embodiments, the pharmaceutical composition is formulated for intravenous injection, oral administration, inhalation, nasal administration, topical administration, or ophthalmic administration. In some embodiments, the pharmaceutical composition is formulated for oral administration. In some embodiments, the pharmaceutical composition is formulated for intravenous injection. In some embodiments, the pharmaceutical composition is formulated as a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye drop, or an ear drop. In some embodiments, the pharmaceutical composition is formulated as a tablet.

Preparation and Characterization of the Compounds

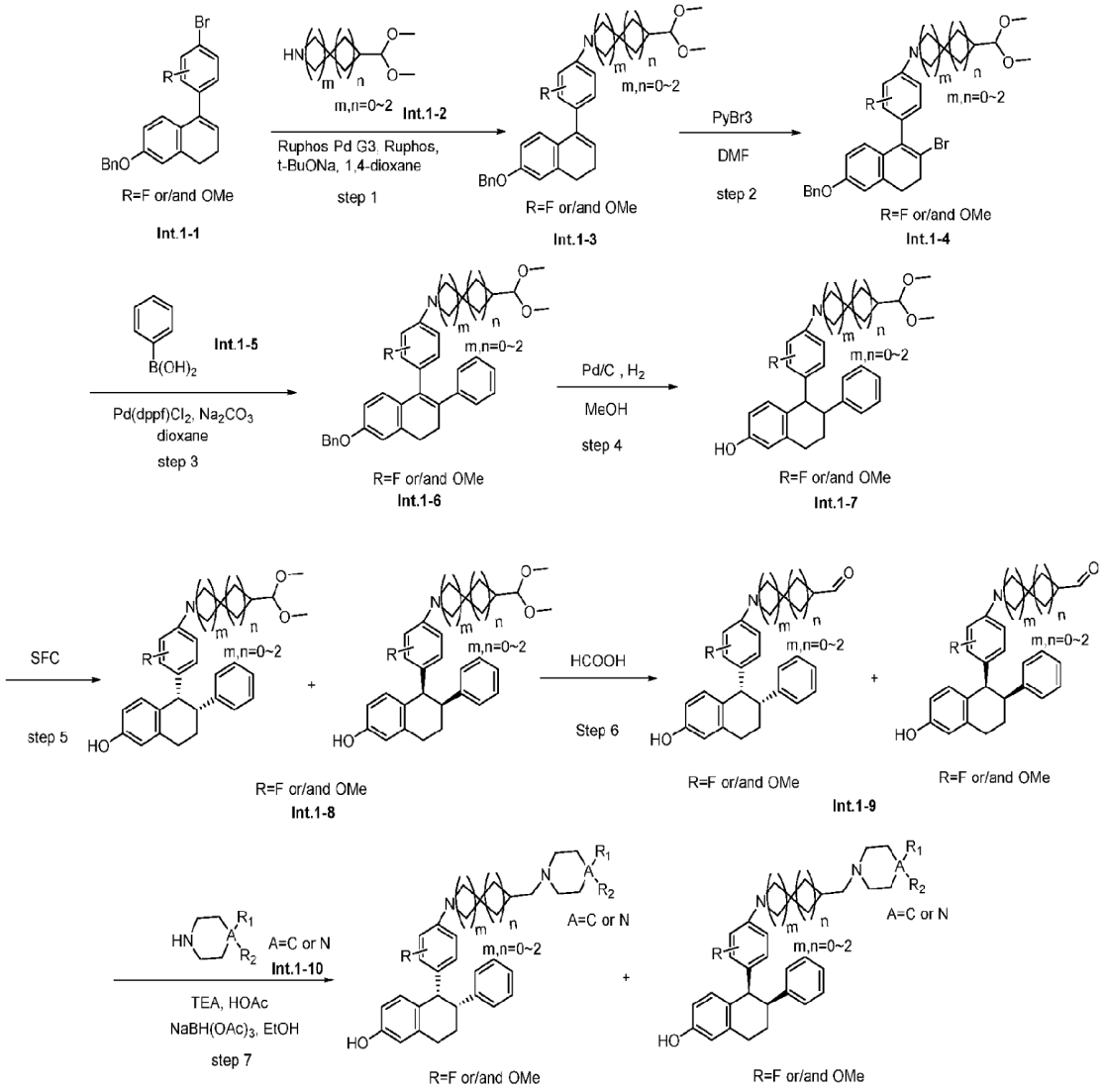
[0233] The compounds of the present disclosure can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, the compounds of the present disclosure can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. The compounds of the present disclosure (*i.e.*, a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein)) can be synthesized by following the general synthetic scheme below as well as the steps outlined in the examples, schemes, procedures, and/or synthesis described herein (*e.g.*, Examples).

General Synthetic Method

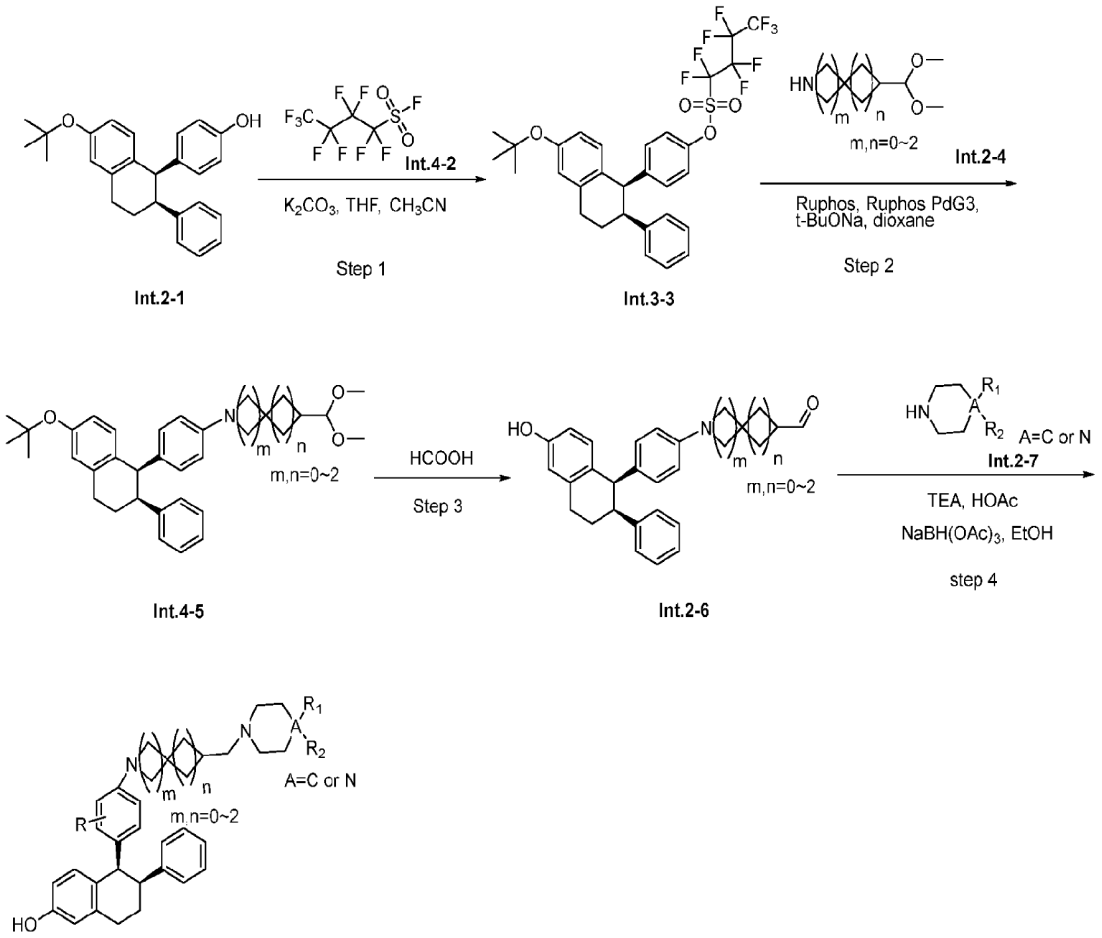
[0234] The compounds of the present disclosure can generally be prepared by first preparing pools of intermediates, including a pool of cereblon ligands, a pool of linkers, and a pool of inhibitors, as detailed in the Example section, then followed by subsequent reactions to connect a linker to an inhibitor and a cereblon ligand via metal-catalyzed coupling reactions and reductive amination. Large pool of compounds can be prepared by selecting different combinations of cereblon ligands,

linkers, and inhibitors from each pool. General synthetic routes for preparing inhibitor-linker conjugate via metal-catalyzed coupling reactions, which is further coupled to cerebon ligand via reductive amination, are summarize below.

Scheme 1



Scheme 2



[0235] Those skilled in the art will recognize if a stereocenter exists in the compounds of the present dislosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein). Accordingly, the present disclosure includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compound but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. *See*, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-lnterscience, 1994).

[0236] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh,

PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH, Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chem Service Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and Wako Chemicals USA, Inc. (Richmond, VA).

[0237] Suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley &

Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

[0238] Specific and analogous reactants are optionally identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line. Chemicals that are known but not commercially available in catalogs are optionally prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

Analytical Methods, Materials, and Instrumentation

[0239] Unless otherwise noted, reagents and solvents are used as received from commercial suppliers. Proton nuclear magnetic resonance (NMR) spectra were obtained on either Bruker or Varian spectrometers at 400 MHz. Spectra are given in ppm (δ) and coupling constants, J, are reported in Hertz. Tetramethylsilane (TMS) was used as an internal standard. Liquid chromatography-mass spectrometry (LC/MS) were collected using a SHIMADZU LCMS-2020EV or Agilent 1260-6125B LCMS. Purity and low-resolution mass spectral data were measured using Agilent 1260-6125B LCMS system (with Diode Array Detector, and Agilent G6125BA Mass spectrometer) or using Waters Acquity UPLC system (with Diode Array Detector, and Waters 3100 Mass Detector). The purity was characterized by UV wavelength 214 nm, 220 nm, 254 nm and ESI. Column: poroshell 120 EC-C18 2.7 μm 4.6 X 100 mm; Flow rate 0.8 mL/min; Solvent A (100/0.1 water/formic acid), Solvent B (100 acetonitrile); gradient: hold 5% B to 0.3 min, 5-95% B from 0.3 to 2 min, hold 95% B to 4.8 min, 95-5% B from 4.8 to 5.4 min, then hold 5% B to 6.5 min. Or, column: Acquity UPLC BEH C18 1.7 μm 2.1 X 50 mm; Flow rate 0.5 mL/min; Solvent A (0.1%formic acid water), Solvent B (acetonitrile); gradient: hold 5%B for 0.2 min, 5-95% B from 0.2 to 2.0 min, hold 95% B to 3.1 min, then 5% B at 3.5 min.

Biological Assays

[0240] The biological activities of the compounds of the present application can be assessed with methods and assays known in the art.

[0241] The CRBN-DDB1 binding potency of the present disclosure is determined using HTRF assay technology (Perkin Elmer). Compounds are serially diluted and are transferred multi-well plate. The reaction is conducted with addition of His-tagged (e.g., CRBN+DDB-DLS7+CXU4) followed by addition of 60 nM fluorescent probe (e.g., Cy5-labeled Thalidomide), and MAb Anti-6HIS Tb cryptate Gold in the assay buffer. After one hour incubation at room temperature, the HTRF signals are read, e.g., on Envision reader (Perkin Elemer).

[0242] ERa degradative activity of compounds can be assessed in MCF-7 and T47D Cells. MCF-7 and T47D cell are seeded and are subsequently treated with the compounds at certain concentrations (e.g., 0.02 to 300 nM). DMSO can be used as vehicle control. Cells are fixed and are blocked with Intercept (PBS) Blocking Buffer (e.g., Li-COR, Odyssey Blocking Buffer), and are stained with ER (e.g., 1:500, Cell signaling) primary antibody for overnight in a cold room (e.g., 4 °C). Secondary Antibody (*e.g.,* IRDye 800CW Goat anti-Rabbit IgG) and CellTag 700 Stain are added in Intercept (PBS) Blocking Buffer. Finally, cell plate is placed in incubator to dry. Image and signal were captured on Odyssey® DLx Imaging System.

[0243] An in vitro assay can be accompolished by an MCF-7 and T47D Cell Titer Glo (CTG) assay. MCF-7 and T47D cell (From HDB) are cultured in a multi-well white plate with phenol red-free RPMI1640 + 10% CS-FBS + 1% P/S medium (e.g., at 1,000cells/well). On day 0, cells were treated with compound at certain concentrations (e.g., 0.5 to 10000 nM) (DMSO and Staurosporine as control). On day 0 and day 6 Cell Titer Glo reagent is added and read on EnVision after 30min incubation for data generation.

[0244] For in-cell western blot analysis, cells are seeded in multi-well plates (e.g., at 40,000 or 10,000 cells/well). Diluted compounds at certain concentration are added (final 0.5% DMSO) and cells are incubated for certain period of time (e.g., 16 hours). Formaldehyde (e.g., PBS:FA=9:1) is added and followed by washing with PBS. The cells are blocked with Licor blocking buffer (Li-Cor). The relative ER percentage in treated cells is obtained by comparing the values of treated wells to those in untreated and DMSO-treated wells as 100%.

[0245] For western blot analysis, cells that are treated with the compounds are lysed in Radioimmunoprecipitation Assay Protein Lysis and Extraction Buffer (e.g., 25 mmol/L Tris.HCl, pH 7.6, 150 mmol/L NaCl, 1% Nonidet P-40, 1% sodium deoxycholate, and 0.1% sodium dodecyl

sulfate) containing proteinase inhibitor cocktail. Equal amounts of total protein are electrophoresed through 10% SDS-polyacrylamide gels after determination of protein concentration by BCA assay. The separated protein bands are transferred onto PVDF membranes and blotted against different antibodies. The blots are scanned, and the band intensities are quantified (e.g., by using GelQuant.NET software provided by biochemlabsolutions.com). The relative mean intensity of target proteins is expressed after normalization to the intensity of glyceraldehyde-3-phosphate dehydrogenase bands.

[0246] For the cell growth assay, cells are seeded at certain concentrations (e.g., at 1500/well) in multi-well plates overnight. Cells are subsequently treated with the compounds. A certain period of time (e.g., 4 days) after the compound treatment, 10% WST-8 reagent is added to the culture medium and incubated under certain condiction (e.g., in a CO_2 incubator at 37 °C for 2.5 hours). The absorbance is measured on each sample using a microplate reader at certain wavelength (e.g., 450 nm). The relative absorbance is calculated against the vehicle control from three individually repeats.

[0247] For in vivo pharmacodynamic and efficacy studies, breast cancer cell line xenografts are developed as follows: mice are given 17β-Estradiol in drinking water for a certain period of time. A certain number (e.g., five million) of cells in 50% Matrigel are injected subcutaneously into SCID mice to induce tumor formation. When tumors reach a certain size (e.g., 100-400 mm^3), mice are treated with vehicle control (e.g., 5% DMSO, 10% solutol, 85% water) or the compound, and sacrificed at various time points. Tumor tissue is harvested for analysis. Tumor sizes and animal weights are measured 2-3 times per week. Tumor volume (mm^3) = (length×width2)/2. Tumor growth inhibition is calculated using TGI (%) = (Vc−Vt)/(Vc−Vo) × 100, where Vc, Vt are the median of control and treated groups at the end of the study and Vo at the start.

Methods of Use

[0248] In certain aspects, the present disclosure provides methods of degrading an estrogen receptor in a subject, comprising administering to the subject a compound disclosed herein.

[0249] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for degrading an estrogen receptor in a subject.

[0250] In certain aspects, the present disclsoure provides compounds disclosed herein for use in degrading an estrogen receptor in a subject.

[0251] In certain aspects, the present disclosure provides methods of treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject a compound disclosed herein (e.g., in a therapeutically effective amount).

[0252] In certain aspects, the present disclosure provides methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a compound disclosed herein (e.g., in a therapeutically effective amount).

[0253] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating or preventing a disease or disorder in a subject in need thereof.

[0254] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

[0255] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating or preventing a disease or disorder in a subject in need thereof.

[0256] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating a disease or disorder in a subject in need thereof.

[0257] In certain embodiments, the disease or disorder is an estrogen receptor-mediated disease or disorder.

[0258] In certain embodiments, the disease or disorder is cancer.

[0259] In certain embodiments, the disease or disorder is breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or esophageal cancer.

[0260] In certain embodiments, the cancer includes, but are not limited to, one or more of the cancers of **Table A**.

Table A.

adrenal cancer	acinic cell carcinoma	acoustic neuroma	acral lentigious melanoma
acrospiroma	acute eosinophilic leukemia	acute erythroid leukemia	acute lymphoblastic leukemia
acute megakaryoblastic leukemia	acute monocytic leukemia	acute promyelocytic leukemia	adenocarcinoma
adenoid cystic carcinoma	adenoma	adenomatoid odontogenic tumor	adenosquamous carcinoma
adipose tissue neoplasm	adrenocortical carcinoma	adult T-cell leukemia/lymphoma	aggressive NK-cell leukemia

AIDS-related lymphoma	alveolar rhabdomyosarcoma	alveolar soft part sarcoma	ameloblastic fibroma
anaplastic large cell lymphoma	anaplastic thyroid cancer	angioimmunoblastic T-cell lymphoma	angiomyolipoma
angiosarcoma	astrocytoma	atypical teratoid rhabdoid tumor	B-cell chronic lymphocytic leukemia
B-cell prolymphocytic leukemia	B-cell lymphoma	basal cell carcinoma	biliary tract cancer
bladder cancer	blastoma	bone cancer	Brenner tumor
Brown tumor	Burkitt's lymphoma	breast cancer	brain cancer
carcinoma	carcinoma in situ	carcinosarcoma	cartilage tumor
cementoma	myeloid sarcoma	chondroma	chordoma
choriocarcinoma	choroid plexus papilloma	clear-cell sarcoma of the kidney	craniopharyngioma
cutaneous T-cell lymphoma	cervical cancer	colorectal cancer	Degos disease
desmoplastic small round cell tumor	diffuse large B-cell lymphoma	dysembryoplastic neuroepithelial tumor	dysgerminoma
embryonal carcinoma	endocrine gland neoplasm	endodermal sinus tumor	enteropathy-associated T-cell lymphoma
esophageal cancer	fetus in fetu	fibroma	fibrosarcoma
follicular lymphoma	follicular thyroid cancer	ganglioneuroma	gastrointestinal cancer
germ cell tumor	gestational choriocarcinoma	giant cell fibroblastoma	giant cell tumor of the bone
glial tumor	glioblastoma multiforme	glioma	gliomatosis cerebri
glucagonoma	gonadoblastoma	granulosa cell tumor	gynandroblastoma
gallbladder cancer	gastric cancer	hairy cell leukemia	hemangioblastoma
head and neck cancer	hemangiopericytoma	hematological cancer	hepatoblastoma
hepatosplenic T-cell lymphoma	Hodgkin's lymphoma	non-Hodgkin's lymphoma	invasive lobular carcinoma

intestinal cancer	kidney cancer	laryngeal cancer	lentigo maligna
lethal midline carcinoma	leukemia	leydig cell tumor	liposarcoma
lung cancer	lymphangioma	lymphangiosarcoma	lymphoepithelioma
lymphoma	acute lymphocytic leukemia	acute myelogeous leukemia	chronic lymphocytic leukemia
liver cancer	small cell lung cancer	non-small cell lung cancer	MALT lymphoma
malignant fibrous histiocytoma	malignant peripheral nerve sheath tumor	malignant triton tumor	mantle cell lymphoma
marginal zone B-cell lymphoma	mast cell leukemia	mediastinal germ cell tumor	medullary carcinoma of the breast
medullary thyroid cancer	medulloblastoma	melanoma	meningioma
merkel cell cancer	mesothelioma	metastatic urothelial carcinoma	mixed Mullerian tumor
mucinous tumor	multiple myeloma	muscle tissue neoplasm	mycosis fungoides
myxoid liposarcoma	myxoma	myxosarcoma	nasopharyngeal carcinoma
neurinoma	neuroblastoma	neurofibroma	neuroma
nodular melanoma	ocular cancer	oligoastrocytoma	oligodendroglioma
oncocytoma	optic nerve sheath meningioma	optic nerve tumor	oral cancer
osteosarcoma	ovarian cancer	Pancoast tumor	papillary thyroid cancer
paraganglioma	pinealoblastoma	pineocytoma	pituicytoma
pituitary adenoma	pituitary tumor	plasmacytoma	polyembryoma
precursor T-lymphoblastic lymphoma	primary central nervous system lymphoma	primary effusion lymphoma	preimary peritoneal cancer
prostate cancer	pancreatic cancer	pharyngeal cancer	pseudomyxoma periotonei
renal cell carcinoma	renal medullary carcinoma	retinoblastoma	rhabdomyoma
rhabdomyosarcoma	Richter's transformation	rectal cancer	sarcoma

Schwannomatosis	seminoma	Sertoli cell tumor	sex cord-gonadal stromal tumor
signet ring cell carcinoma	skin cancer	small blue round cell tumors	small cell carcinoma
soft tissue sarcoma	somatostatinoma	soot wart	spinal tumor
splenic marginal zone lymphoma	squamous cell carcinoma	synovial sarcoma	Sezary's disease
small intestine cancer	squamous carcinoma	stomach cancer	T-cell lymphoma
testicular cancer	thecoma	thyroid cancer	transitional cell carcinoma
throat cancer	urachal cancer	urogenital cancer	urothelial carcinoma
uveal melanoma	uterine cancer	verrucous carcinoma	visual pathway glioma
vulvar cancer	vaginal cancer	Waldenstrom's macroglobulinemia	Warthin's tumor
Wilms' tumor			

[0261] In certain embodiments, the cancer is a solid tumor. In certain embodiments, the cancer a hematological cancer. Exemplary hematological cancers include, but are not limited to, the cancers listed in **Table B**. In certain embodiments, the hematological cancer is acute lymphocytic leukemia, chronic lymphocytic leukemia (including B-cell chronic lymphocytic leukemia), or acute myeloid leukemia.

Table B.

acute lymphocytic leukemia (ALL)	acute eosinophilic leukemia
acute myeloid leukemia (AML)	acute erythroid leukemia
chronic lymphocytic leukemia (CLL)	acute lymphoblastic leukemia
small lymphocytic lymphoma (SLL)	acute megakaryoblastic leukemia
multiple myeloma (MM)	acute monocytic leukemia
Hodgkins lymphoma (HL)	acute promyelocytic leukemia
non-Hodgkin's lymphoma (NHL)	acute myelogeous leukemia
mantle cell lymphoma (MCL)	B-cell prolymphocytic leukemia
marginal zone B-cell lymphoma	B-cell lymphoma

splenic marginal zone lymphoma	MALT lymphoma
follicular lymphoma (FL)	precursor T-lymphoblastic lymphoma
Waldenstrom's macroglobulinemia (WM)	T-cell lymphoma
diffuse large B-cell lymphoma (DLBCL)	mast cell leukemia
marginal zone lymphoma (MZL)	adult T cell leukemia/lymphoma
hairy cell leukemia (HCL)	aggressive NK-cell leukemia
Burkitt's lymphoma (BL)	angioimmunoblastic T-cell lymphoma
Richter's transformation	

[0262] In certain embodiments, the subject is a mammal.

[0263] In certain embodiments, the subject is a human.

Definitions

[0264] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

Chemical Definitions

[0265] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, Organic Chemistry, University Science Books, Sausalito, 1999; Smith and March, March's Advanced Organic Chemistry, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, Comprehensive Organic Transformations, VCH Publishers, Inc., New York, 1989; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0266] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.,* enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography

(HPFC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. *See*, for example, Jacques et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen et al., Tetrahedron 33:2725 (1977); Eliel, Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, Tables of Resolving Agents and Optical Resolutions p. 268 (E.F. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[0267] The disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0268] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0269] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present disclosure. When describing the disclosure, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term "substituted" is to be defined as set out below. It should be further understood that the terms "groups" and "radicals" can be considered interchangeable when used herein. The articles "a" and "an" may be used herein to refer to one or more than one (*i.e.,* at least one) of the grammatical objects of the article. By way of example "an analogue" means one analogue or more than one analogue.

[0270] "Alkyl" as used herein, refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C_{1-20} alkyl"). In certain embodiments, an alkyl group has 1 to 12 carbon atoms ("C_{1-12} alkyl"). In certain embodiments, an alkyl group has 1 to 10 carbon atoms ("C_{1-10} alkyl"). In certain embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In certain embodiments, an alkyl group has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In certain embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In certain embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl", which is also referred to herein

as "lower alkyl"). In certain embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In certain embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In certain embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In certain embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In certain embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), *n*-propyl (C_3), isopropyl (C_3), *n*-butyl (C_4), *tert*-butyl (C_4), *sec*-butyl (C_4), isobutyl (C_4), *n*-pentyl (C_5), 3-pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3-methyl-2-butanyl (C_5), tertiary amyl (C_5), and *n*-hexyl (C_6). Additional examples of alkyl groups include *n*-heptyl (C_7), *n*-octyl (C_8) and the like. Unless otherwise specified, each instance of an alkyl group is independently optionally substituted, i.e., unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents; e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkyl group is unsubstituted C_{1-10} alkyl (e.g., $-CH_3$). In certain embodiments, the alkyl group is substituted C_{1-10} alkyl. Common alkyl abbreviations include Me ($-CH_3$), Et ($-CH_2CH_3$), *i*-Pr ($-CH(CH_3)_2$), *n*-Pr ($-CH_2CH_2CH_3$), *n*-Bu ($-CH_2CH_2CH_2CH_3$), or *i*-Bu ($-CH_2CH(CH_3)_2$).

[0271] "Alkylene" as used herein, refers to an alkyl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of carbons is provided for a particular "alkylene" group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. An "alkelene" group may be substituted or unsubstituted with one or more substituents as described herein. Exemplary unsubstituted divalent alkylene groups include, but are not limited to, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), butylene ($-CH_2CH_2CH_2CH_2-$), pentylene ($-CH_2CH_2CH_2CH_2CH_2-$), hexylene ($-CH_2CH_2CH_2CH_2CH_2CH_2-$), and the like. Exemplary substituted divalent alkylene groups, e.g., substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted methylene ($-CH(CH_3)-$, ($-C(CH_3)_2-$), substituted ethylene ($-CH(CH_3)CH_2-$,$-CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2-$,$-CH_2C(CH_3)_2-$), substituted propylene ($-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2CH_2-$, $-CH_2C(CH3)_2CH_2-$, $-CH_2CH_2C(CH_3)_2-$), and the like.

[0272] "Alkenyl" as used herein, refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon double bonds), and optionally one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon triple bonds) ("C_{2-20} alkenyl"). In certain embodiments, alkenyl does not

contain any triple bonds. In certain embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_{2-10} alkenyl"). In certain embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In certain embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In certain embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In certain embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In certain embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In certain embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In certain embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In certain embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, i.e., unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkenyl group is unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-10} alkenyl.

[0273] "Alkenylene" as used herein, refers to an alkenyl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of carbons is provided for a particular "alkenylene" group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. An "alkenylene" group may be substituted or unsubstituted with one or more substituents as described herein. Exemplary unsubstituted divalent alkenylene groups include, but are not limited to, ethenylene (-CH=CH-) and propenylene (*e.g.*, -CH=CHCH$_2$-, -CH$_2$-CH=CH-). Exemplary substituted divalent alkenylene groups, e.g., substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted ethylene (-C(CH$_3$)=CH-, -CH=C(CH$_3$)-), substituted propylene (*e.g.*, -C(CH$_3$)=CHCH$_2$-, -CH=C(CH$_3$)CH$_2$-, -CH=CHCH(CH$_3$)-, -CH=CHC(CH$_3$)$_2$-, -CH(CH$_3$)-CH=CH-,-C(CH$_3$)$_2$-CH=CH-, -CH$_2$-C(CH$_3$)=CH-, -CH$_2$-CH=C(CH$_3$)-), and the like.

[0274] "Alkynyl" as used herein, refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or

4 carbon-carbon triple bonds), and optionally one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon double bonds) ("C_{2-20} alkynyl"). In certain embodiments, alkynyl does not contain any double bonds. In certain embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_{2-10} alkynyl"). In certain embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In certain embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In certain embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In certain embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In certain embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In certain embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In certain embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In certain embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon-carbon triple bonds can be internal (such as in 2-butynyl) or terminal (such as in 1-butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently optionally substituted, i.e., unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents; e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkynyl group is unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-10} alkynyl.

[0275] "Alkynylene" as used herein, refers to a alkynyl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of carbons is provided for a particular "alkynylene" group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. An "alkynylene" group may be substituted or unsubstituted with one or more substituents as described herein. Exemplary divalent alkynylene groups include, but are not limited to, substituted or unsubstituted ethynylene, substituted or unsubstituted propynylene, and the like.

[0276] The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, which further comprises 1 or more (*e.g.*, 1, 2, 3, or 4) heteroatoms (*e.g.*, oxygen, sulfur, nitrogen, boron, silicon, phosphorus) within the parent chain, wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is

inserted between a carbon atom and the parent molecule, i.e., between the point of attachment. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon atoms and 1, 2, 3, or 4 heteroatoms ("C_{1-10} heteroalkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1, 2, 3, or 4 heteroatoms ("C_{1-9} heteroalkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1, 2, 3, or 4 heteroatoms ("C_{1-8} heteroalkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1, 2, 3, or 4 heteroatoms ("C_{1-7} heteroalkyl"). In certain embodiments, a heteroalkyl group is a group having 1 to 6 carbon atoms and 1, 2, or 3 heteroatoms ("C_{1-6} heteroalkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms ("C_{1-5} heteroalkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and/or 2 heteroatoms ("C_{1-4} heteroalkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom ("C_{1-3} heteroalkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom ("C_{1-2} heteroalkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("C_1 heteroalkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms ("C_{2-6} heteroalkyl"). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted C_{1-10} heteroalkyl. In certain embodiments, the heteroalkyl group is a substituted C_{1-10} heteroalkyl.

[0277] The term "heteroalkenyl," as used herein, refers to an alkenyl group, as defined herein, which further comprises one or more (*e.g.,* 1, 2, 3, or 4) heteroatoms (*e.g.,* oxygen, sulfur, nitrogen, boron, silicon, phosphorus) wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is inserted between a carbon atom and the parent molecule, i.e., between the point of attachment. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms ("C_{2-10} heteroalkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1, 2, 3, or 4 heteroatoms ("C_{2-9} heteroalkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms ("C_{2-8} heteroalkenyl"). In certain embodiments,

a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms ("C_{2-7} heteroalkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1, 2, or 3 heteroatoms ("C_{2-6} heteroalkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms ("C_{2-5} heteroalkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms ("C_{2-4} heteroalkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom ("C_{2-3} heteroalkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms ("C_{2-6} heteroalkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted C_{2-10} heteroalkenyl. In certain embodiments, the heteroalkenyl group is a substituted C_{2-10} heteroalkenyl.

[0278] The term "heteroalkynyl," as used herein, refers to an alkynyl group, as defined herein, which further comprises one or more (*e.g.,* 1, 2, 3, or 4) heteroatoms (*e.g.,* oxygen, sulfur, nitrogen, boron, silicon, phosphorus) wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms are inserted between a carbon atom and the parent molecule, *i.e.,* between the point of attachment. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("C_{2-10} heteroalkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("C_{2-9} heteroalkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("C_{2-8} heteroalkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("C_{2-7} heteroalkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1, 2, or 3 heteroatoms ("C_{2-6} heteroalkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms ("C_{2-5} heteroalkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and lor 2 heteroatoms ("C_{2-4} heteroalkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom ("C_{2-3} heteroalkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least

one triple bond, and 1 or 2 heteroatoms ("C_{2-6} heteroalkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted C_{2-10} heteroalkynyl. In certain embodiments, the heteroalkynyl group is a substituted C_{2-10} heteroalkynyl.

[0279] Analogous to "alkylene," "alkenylene," and "alkynylene" as defined above, "heteroalkylene," "heteroalkenylene," and "heteroalkynylene," as used herein, refer to a divalent radical of heteroalkyl, heteroalkenyl, and heteroalkynyl group respectively. When a range or number of carbons is provided for a particular "heteroalkylene," "heteroalkenylene," or "heteroalkynylene," group, it is understood that the range or number refers to the range or number of carbons in the linear divalent chain. "Heteroalkylene," "heteroalkenylene," and "heteroalkynylene" groups may be substituted or unsubstituted with one or more substituents as described herein.

[0280] "Aryl" refers to a radical of a monocyclic or polycyclic (e.g., bicyclic or tricyclic) 4n+2 aromatic ring system (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; e.g., phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; e.g., anthracyl). Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, and trinaphthalene. Particular aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl. Unless otherwise specified, each instance of an aryl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is substituted C_{6-14} aryl.

[0281] "Heteroaryl" refers to a radical of a 5- to 14-membered monocyclic or polycyclic 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring

carbon atoms and 1-8 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5- to 14-membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings.

[0282] "Heteroaryl" also includes ring systems wherein the heteroaryl group, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the heteroaryl or the one or more aryl groups, and in such instances, the number of ring members designates the total number of ring members in the fused (aryl/heteroaryl) ring system. When substitution is indicated in such instances, unless otherwise specified, substitution can occur on either the heteroaryl or the one or more aryl groups. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.,* either the ring bearing a heteroatom (*e.g.,* 2-indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5-indolyl).

[0283] In certain embodiments, a heteroaryl is a 5- to 10-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5- to 10-membered heteroaryl"). In certain embodiments, a heteroaryl is a 5- to 9-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5- to 9-membered heteroaryl"). In certain embodiments, a heteroaryl is a 5- to 8-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5- to 8-membered heteroaryl"). In certain embodiments, a heteroaryl group is a 5- to 6-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5- to 6-membered heteroaryl"). In certain embodiments, the 5- to 6-membered heteroaryl has 1-3 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heteroaryl has 1-2 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a

heteroaryl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5- to 14-membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5- to 14-membered heteroaryl.

[0284] 5-membered heteroaryl containing one heteroatom includes, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0285] "Carbocyclyl" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 12 ring carbon atoms ("C_{3-12} carbocyclyl") and zero heteroatoms in the nonaromatic ring system. In certain embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In certain embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In certain embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 to 12 ring carbon atoms ("C_{5-12} carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 to 8 ring carbon atoms ("C_{5-8} carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 or 6 ring carbon atoms ("C_{5-6} carbocyclyl"). Exemplary C_{3-6} carbocyclyl include, without limitation, cyclopropyl (C_3),

cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like.

[0286] In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 12 ring carbon atoms ("C_{3-12} carbocyclyl"). In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 5 to 12 ring carbon atoms ("C_{5-12} carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 to 8 ring carbon atoms ("C_{5-8} carbocyclyl"). In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having 5 or 6 ring carbon atoms ("C_{5-6} carbocyclyl"). Examples of C_{5-6} carbocyclyl include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} carbocyclyl include the aforementioned C_{5-6} carbocyclyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} carbocyclyl include the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C_{3-12} carbocyclyl. In certain embodiments, the carbocyclyl group is substituted C_{3-12} carbocyclyl.

[0287] In certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or polycyclic ("polycyclic carbocyclyl") that contains a fused, bridged or spiro ring system and can be saturated or can be partially unsaturated. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, i.e., unsubstituted (an

"unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C_{3-12} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-12} carbocyclyl.

[0288] "Fused carbocyclyl" or "fused carbocycle" refers to ring systems wherein the carbocyclyl group, as defined above, is fused with, i.e., share one common bond with, one or more carbocyclyl groups, as defined above, wherein the point of attachment is on any of the fused rings. In such instances, the number of carbons designates the total number of carbons in the fused carbocyclyl ring system. When substitution is indicated, unless otherwise specified, substitution can occur on any of the fused rings.

[0289] "Spiro carbocyclyl" or or "spiro carbocycle" refers to ring systems wherein the carbocyclyl group, as defined above, form spiro structure with, i.e., share one common atom with, one or more carbocyclyl groups, as defined above, wherein the point of attachment is on any of the carbocyclyl rings in which the spiro structure is embeded. In such instances, the number of carbons designates the total number of carbons of the carbocyclyl rings in which the spiro structure is embeded. When substitution is indicated, unless otherwise specified, substitution can occur on any of the carbocyclyl rings in which the spiro structure is embeded.

[0290] "Bridged carbocyclyl" or or "bridged carbocycle" refers to ring systems wherein the carbocyclyl group, as defined above, form bridged structure with, i.e., share more than one atoms (as such, share more than one bonds) with, one or more carbocyclyl groups, as defined above, wherein the point of attachment is on any of the carbocyclyl rings in which the bridged structure is embeded. In such instances, the number of carbons designates the total number of carbons of the bridged rings. When substitution is indicated, unless otherwise specified, substitution can occur on any of the carbocyclyl rings in which the bridged structure is embeded.

[0291] "Heterocyclyl" refers to a radical of a 3- to 12-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("3- to 12-membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5membered heterocyclyl groups containing one

heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0292] In certain embodiments, a heterocyclyl group is a 5- to 12-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("5- to 12-membered heterocyclyl"). In certain embodiments, a heterocyclyl group is a 5- to 10-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("5- to 10-membered heterocyclyl"). In certain embodiments, a heterocyclyl group is a 5- to 8-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5- to 8-membered heterocyclyl"). In certain embodiments, a heterocyclyl group is a 5- to 6-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5- to 6-membered heterocyclyl"). In certain embodiments, the 5- to 6-membered heterocyclyl has 1-3 ring heteroatoms selected from

nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heterocyclyl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0293] In certain embodiments, a heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or polycyclic ("polycyclic heterocyclyl") that contains a fused, bridged or spiro ring system, and can be saturated or can be partially unsaturated. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl group, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, and in such instances, the number of ring members designates the total number of ring members in the entire ring system. When substitution is indicated in such instances, unless otherwise specified, substitution can occur on either the heterocyclyl or the one or more carbocyclyl groups. Unless otherwise specified, each instance of heterocyclyl is independently optionally substituted, i.e., unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3- to 12-membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3- to 12-membered heterocyclyl.

[0294] "Fused heterocyclyl" or "fused heterocycle" refers to ring systems wherein the heterocyclyl group, as defined above, is fused with, i.e., share one common bond with, one or more heterocyclyl or carbocyclyl groups, as defined above, wherein the point of attachment is on any of the fused rings. In such instances, the number of carbons designates the total number of ring members in the fused ring system. When substitution is indicated, unless otherwise specified, substitution can occur on any of the fused rings.

[0295] "Spiro heterocyclyl" or "spiro heterocycle" refers to ring systems wherein the heterocyclyl group, as defined above, form spiro structure with, i.e., share one common atom with, one or more heterocyclyl or carbocyclyl groups, as defined above, wherein the point of attachment is on the heterocyclyl or carbocyclyl rings in which the spiro structure is embeded. In such instances, the number of ring members designates the total number of ring members of the heterocyclyl or carbocyclyl rings in which the spiro structure is embeded. When substitution is indicated, unless otherwise specified, substitution can occur on any of the heterocyclyl or carbocyclyl rings in which the spiro structure is embeded.

[0296] "Bridged heterocyclyl" or "bridged heterocycle" refers to ring systems wherein the heterocyclyl group, as defined above, form bridged structure with, i.e., share more than one atoms (as such, share more than one bonds) with, one or more heterocyclyl or carbocyclyl groups, as defined above, wherein the point of attachment is on the heterocyclyl or carbocyclyl rings in which the bridged structure is embeded. In such instances, the number of ring members designates the total number of ring members of the heterocyclyl or carbocyclyl rings in which the bridged structure is embeded. When substitution is indicated, unless otherwise specified, substitution can occur on any of the bridged rings.

[0297] "Hetero" when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, sulfur, boron, phosphorus, or silicon heteroatom, as valency permits. Hetero may be applied to any of the hydrocarbyl groups described above having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[0298] "Alkoxy" as used herein, refers to the group -OR, wherein R is alkyl as defined herein. C_{1-6} alkoxy refers to the group -OR, wherein each R is C_{1-6} alkyl, as defined herein. Exemplary C_{1-6} alkyl is set forth above.

[0299] "Alkylamino" as used herein, refers to the group -NHR or $-NR_2$, wherein each R is independently alkyl, as defined herein. C_{1-6} alkylamino refers to the group -NHR or $-NR_2$, wherein each R is independently C_{1-6} alkyl, as defined herein. Exemplary C_{1-6} alkyl is set forth above.

[0300] "Oxo" refers to =O. When a group other than aryl and heteroaryl or an atom is substituted with an oxo, it is meant to indicate that two geminal radicals on that group or atom form a double bond with an oxygen radical. When a heteroaryl is substituted with an oxo, it is meant to indicate that a resonance structure/tautomer involving a heteroatom provides a carbon atom that is able to form two geminal radicals, which form a double bond with an oxygen radical.

[0301] "Halo" or "halogen" refers to fluoro (F), chloro (Cl), bromo (Br), and iodo (I). In certain embodiments, the halo group is either fluoro or chloro.

[0302] "Protecting group" as used herein is art-recognized and refers to a chemical moiety introduced into a molecule by chemical modification of a functional group (e.g., hydroxyl, amino, thio, and carboxylic acid) to obtain chemoselectivity in a subsequent chemical reaction, during which the unmodified functional group may not survive or may interfere with the chemical reaction. Common functional groups that need to be protected include but not limited to hydroxyl,

amino, thiol, and carboxylic acid. Accordingly, the protecting groups are termed hydroxyl-protecting groups, amino-protecting groups, thiol-protecting groups, and carboxylic acid-protecting groups, respectively.

[0303] Common types of hydroxyl-protecting groups include but not limited to ethers (*e.g.*, methoxymethyl (MOM), β-Methoxyethoxymethyl (MEM), tetrahydropyranyl (THP), *p*-methoxyphenyl (PMP), *t*-butyl, triphenylmethyl (Trityl), allyl, and benzyl ether (Bn)), silyl ethers (*e.g.*, *t*-butyldiphenylsilyl (TBDPS), trimethylsilyl (TMS), triisopropylsilyl (TIPS), tri-*iso*-propylsilyloxymethyl (TOM), and *t*-butyldimethylsilyl (TBDMS)), and esters (*e.g.*, pivalic acid ester (Piv) and benzoic acid ester (benzoate; Bz)).

[0304] Common types of amino-protecting groups include but not limited to carbamates (*e.g.*, *t*-butyloxycarbonyl (Boc), 9-fluorenylmethyloxycarbonyl (Fmoc), *p*-methoxybenzyl carbonyl (Moz or MeOZ), 2,2,2-trichloroehtoxycarbonyl (Troc), and benzyl carbamate (Cbz)), esters (*e.g.*, acetyl (Ac); benzoyl (Bz), trifluoroacetyl, and phthalimide), amines (e.g, benzyl (Bn), *p*-methoxybenzyl (PMB), *p*-methoxyphenyl (PMP), and triphenylmethyl (trityl)), and sulfonamides (*e.g.*, tosyl (Ts), *N*-alkyl nitrobenzenesulfonamides (Nosyl), and 2-nitrophenylsulfenyl (Nps)).

[0305] Common types of thiol-protecting groups include but not limited to sulfide (*e.g.*, p-methylbenzyl (Meb), *t*-butyl, acetamidomethyl (Acm), and triphenylmethyl (Trityl)).

[0306] Common types of carboxylic acid-protecting groups include but not limited to esters (*e.g.*, methyl ester, triphenylmethyl (Trityl), *t*-butyl ester, benzyl ester (Bn), S-*t*-butyl ester, silyl esters, and orthoesters) and oxazoline.

[0307] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The disclosure is not intended to be limited in any manner by the above exemplary listing of substituents.

Other Definitions

[0308] "Pharmaceutically acceptable" means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0309] "Pharmaceutically acceptable salt" refers to a salt of a compound of the disclosure that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent

compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and basc addition salts. Spccifically, such salts includc: (1) acid addition salts, formcd with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo [2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid , 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid , gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion , an alkaline earth ion , or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of nontoxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[0310] A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.,* a male or female of any age group, *e.g.,* a pediatric subject (*e.g,* infant, child, adolescent) or an adult subject (*e.g.,* young adult, middle aged adult or senior adult) and/or a non-human animal, *e.g.,* a mammal such as primates (*e.g.,* cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal.

[0311] An "effective amount" means the amount of a compound that, when administered to a subject for treating or preventing a disease, is sufficient to affect such treatment or prevention. The "effective amount" can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated. A "therapeutically effective amount" refers to the effective amount for therapeutic treatment. A "prophylatically effective amount" refers to the effective amount for prophylactic treatment.

[0312] "Preventing", "prevention" or "prophylactic treatment" refers to a reduction in risk of acquiring or developing a disease or disorder (*i.e.,* causing at least one of the clinical symptoms of the disease not to develop in a subject not yet exposed to a disease-causing agent, or in a subject who is predisposed to the disease in advance of disease onset).

[0313] The term "prophylaxis" is related to "prevention," and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization, and the administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[0314] "Treating" or "treatment" or "therapeutic treatment" of any disease or disorder refers, in certain embodiments, to ameliorating the disease or disorder (*i.e.,* arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In certain embodiments, "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In certain embodiments, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.,* stabilization of a discernible symptom), physiologically, (*e.g.,* stabilization of a physical parameter), or both. In a further embodiment, "treating" or "treatment" relates to slowing the progression of the disease.

[0315] The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability or within statistical experimental error, and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. In certain embodiments, the number or numerical range vary by 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, or 15% of the stated number or numerical range. In certain embodiments, the number or numerical range vary by 1%, 2%, 3%, 4%, or 5% of the stated number or numerical range. In certain embodiments, the number or numerical range vary by 1%, 2%, or 3% of the stated number or numerical range.

[0316] The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an

embodiment of any composition of matter, composition, method, or process, or the like, described herein, "consist of" or "consist essentially of" the described features.

[0317] The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with "and/or" should be construed in the same fashion, i.e., "one or more" of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" may refer, in certain embodiments, to A only (optionally including elements other than B); in certain embodiments, to B only (optionally including elements other than A); in certain embodiments, to both A and B (optionally including other elements); etc.

[0318] As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e., "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

[0319] As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least

one of A or B," or, equivalently "at least one of A and/or B") may refer, in certain embodiments, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in certain embodiments, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in certain embodiments, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

[0320] While the present teachings have been described in conjunction with various embodiments and examples, it is not intended that the present teachings be limited to such embodiments or examples. On the contrary, the present teachings encompass various alternatives, modifications, and equivalents, as will be appreciated by those of skill in the art.

[0321] While various inventive embodiments have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the function and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the inventive embodiments described herein. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the inventive teachings is/are used. Those skilled in the art will recognize many equivalents to the specific inventive embodiments described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, inventive embodiments may be practiced otherwise than as specifically described and claimed. Inventive embodiments of the present disclosure are directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the inventive scope of the present disclosure.

[0322] The claims should not be read as limited to the described order or elements unless stated to that effect. It should be understood that various changes in form and detail may be made by one of ordinary skill in the art without departing from the spirit and scope of the appended claims. All embodiments that come within the spirit and scope of the following claims and equivalents thereto

are claimed.

EXAMPLES

[0323] In order that the invention described herein may be more fully understood, the following examples are set forth. The examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

[0324] It is understood that the values presented in the examples are approximate values, and they are subject to instrumental and/or experimental variations.

The following abbreviations were used in descriptions and examples:

[0325] ACN acetonitrile; AIBN azobisisobutyronitrile; BINAP ([1,1'-Binaphthalene]-2,2'-diyl)bis(diphenylphosphane); BPO dibenzoyl peroxide; DCE 1,2-dichloroethane; DCM dichloromethane; DEAD Diethylazodicarboxylate; DIPEA *N,N*-diisopropylethylamine; DMF *N,N*-dimethylformamide; DMA *N,N*-dimethylacetamide; DMSO dimethylsulfoxide; EA ethyl acetate; FA formic acid; HMTA 1,3,5,7-Tetraazaadamantane; hr Hour; hrs Hours; IPA *iso*-propyl alcohol; IPE di-isopropyl ether; K_2CO_3 Potassium carbonate; m-CPBA 3-chlorobenzenecarboperoxoic acid; LC/MS liquid chromatography-mass spectrometry; MeOH methanol; MS mass spectrometry; mL Milliliters; $NaBH_3CN$ Sodium cyanoborohydride; NBS N-bromosuccinimide; NCS N-chlorosuccinimide; NMP N-methyl pyrrolidinone; NMR nuclear magnetic resonance; PE petroleum ether; ppm parts per million; T_3P propanephosphonic acid anhydride; TEA triethylamine; THF tetrahydrofuran

I. SYNTHESIS AND CHARACTERIZATION OF INTERMEDIATES AND "A" COMPOUNDS

[0326] The chemical reagents were purchased from commercial sources (such as Alfa, Acros, Sigma Aldrich, TCI, and Shanghai Chemical Reagent Company), and used without further purification.

[0327] In obtaining the compounds described in the examples below and the corresponding analytical data, the following experimental and analytical protocols were followed unless otherwise indicated.

[0328] A summary of LC-MS methods is shown below.

Method A:

Waters SunFire C18 50*4.6 mm 5um 2.000 ml/min 2.6 min Column Temperature: 40 ℃

Gradient: 5% B hold for 0.2 min, increase to 95 % B within 1.40 min, hold at 95 % B for 0.9 min, then back to 5% B within 0.01 min

Pump A: 0.1% formic acid (FA) and 10% acetonitrile (ACN) in H_2O

Pump B: 0.1%FA and 10% H_2O in ACN.

Method B:

Waters SunFire C18 50*4.6 mm 5um 2.000 ml/min 2.6 min Column Temperature: 40 ℃

Gradient: 5% B hold for 0.2 min, increase to 95 % B within 1.40 min, hold at 95 % B for0.9 min, then back to 5% B within 0.01 min

Pump A: 0.03% trifluoroacetic acid (TFA) in H_2O

Pump B: 0.03% TFA in ACN

Method C:

Column: Sunfire C18 150*4.6 mm 5um 1.00 ml/min Column Temperature: 40 ℃

Gradient: 10% B hold for 1.8 min, increase to 95 % B within 10.2 min, hold at 95 % B for 3.0 min, then back to 10% B within 0.01 min

Pump A: 0.03% TFA in H_2O

Pump B: 0.03% TFA in ACN

Method D:

Column: Luna C18 30*2.0 mm 3um 1.200 ml/min 1.5 min Column Temp.: 50 ℃ 5% B increase to 95 % B within 0.7 min, hold at 95 % B for 0.4 min, back to 5% B within 0.01 min

Pump A: 0.03% TFA in H_2O

Pump B: 0.03% TFA in ACN

Method E:

SunFire C18 50*4.6 mm 5um 2.6 min 2.0 ml/min

Temperature: 40 ℃

Gradient: 10% B increase to 30% B for 0.40 min, increase to 95 % B within 1.60 min, 95% B hold for 0.90 min, back to 10% B within 0.01 min, A70B30

Method F:

SunFire C18 50*4.6 mm 5um 2.6 min 2.0 ml/min

Temperature: 40 ℃

Gradient: 10% B increase to 30% B for 0.40 min, increase to 95 % B within 1.60 min, 95% B hold for 0.90 min, back to 10% B within 0.01 min, A50B50.

[0329] Unless otherwise stated, reaction mixtures were magnetically stirred at room temperature (rt) under a nitrogen atmosphere. Where solutions were "dried," they were generally dried over a drying agent such as Na_2SO_4 or $MgSO_4$. Where mixtures, solutions, and extracts were "concentrated", they were typically concentrated on a rotary evaporator under reduced pressure.

[0330] Compound purification was carried out as needed using a variety of traditional methods including, but not limited to, preparative chromatography under acidic, neutral, or basic conditions using either normal phase or reverse phase HPLC or flash columns or Prep-TLC plates.

[0331] Flash chromatography was performed on a Biotage Isolera One via column with silica gel particles of 200-300 mesh. Analytical and preparative thin-layer chromatography was performed using silica gel 60 GF254 plates. Normal-phase silica gel chromatography (FCC) was also performed on silica gel (SiO_2) using prepacked cartridges.

[0332] Preparative reverse-phase high performance liquid chromatography (RP HPLC) was performed on either:

METHOD 1. Prep-HPLC with Waters-Sunfire C18 21.2x250mmx10um, and mobile phase of 10-20% ACN in water (0.1% HCOOH) over 15 min and then hold at 100% ACN for 5 min, at a flow rate of 20 mL/min. or

METHOD 2.

[0333] Preparative supercritical fluid high performance liquid chromatography (SFC) was performed either on a Waters 150 Prep-SFC system from Waters. The ABPR was set to 100 bar to keep the CO_2 in SF conditions, and the flow rate may verify according to the compound characteristics, with a flow rate ranging from 70g/min to 140 g/min. The column temperature was ambient temperature

[0334] Nuclear magnetic resonance (NMR) spectra were recorded using Brucker AVANCE NEO 400 MHz at around 20 - 30°C unless otherwise specified. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublet; dt, doublet of triplets; bs, broad signal. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. It will be understood that for compounds comprising an exchangeable proton, said proton may or may not be visible on an NMR spectrum

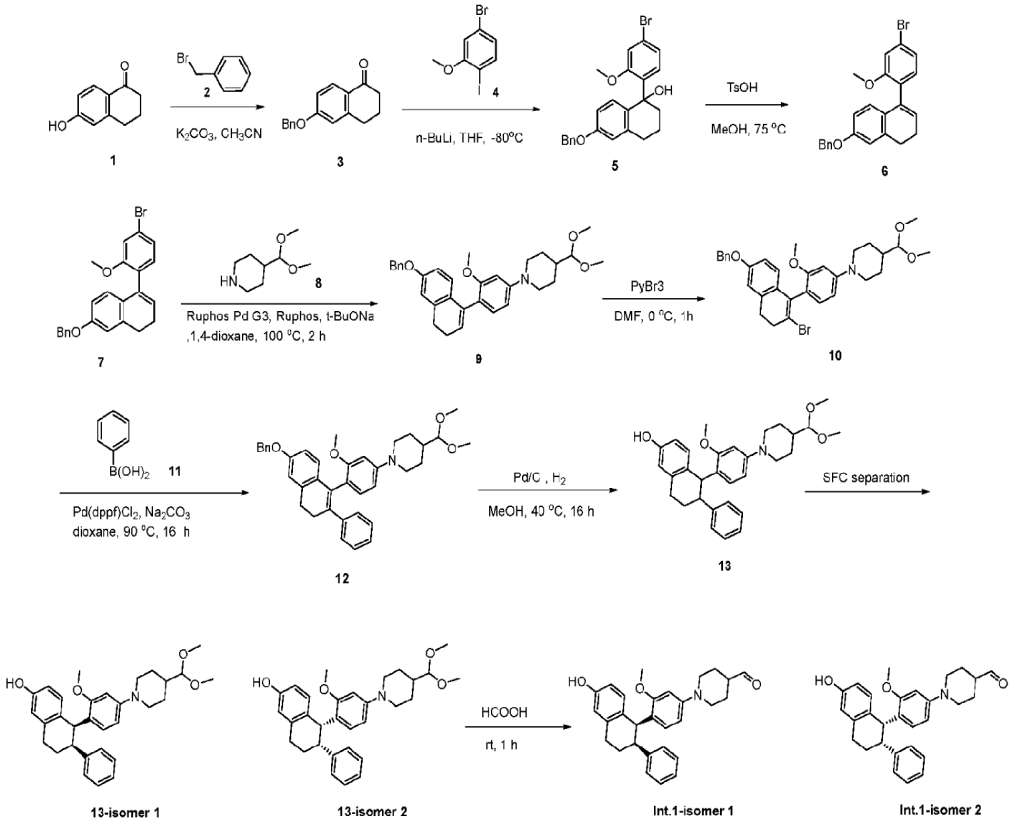
depending on the choice of solvent used for running the NMR spectrum and the concentration of the compound in the solution.

[0335] Mass spectra (MS) were obtained on a SHIMADZU LC-MS-2020 MSD using electrospray ionization (ESI) in positive mode unless otherwise indicated. Calculated (calcd.) mass corresponds to the exact mass.

[0336] Chemical names were generated using ChemDraw Ultra 12.0, ChemDraw Ultra 14.0 (CambridgeSoft Corp., Cambridge, MA) or ACD/Name Version 10.01 (Advanced Chemistry).

[0337] Compounds designated as R* or S* are enantiopure compounds where the absolute configuration was not determined.

Intermediate 1: 1-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-4-(dimethoxymethyl)piperidine



Step 1: 6-(benzyloxy)-3,4-dihydronaphthalen-1(2H)-one

[0338] To a solution of 6-hydroxy-3,4-dihydronaphthalen-1(2H)-one (25 g, 154.14mmol, 1 eq) and K_2CO_3 (46.2 g, 308.28 mmol, 2 eq) in CH_3CN (350 mL) was added BnBr (3.1 g, 184.96 mmol,

1.2 eq) and stirred at 50°C for 2 hours. LCMS showed the reaction was completed. The reaction was concentrated under vacuum to afford the product 6-(benzyloxy)-3,4-dihydronaphthalen-1(2H)-one (30.3 g,78%). LC−MS purity 100% (UV at 254 nm), 253 $[M+H]^+$.

Step 2: 6-(benzyloxy)-1-(4-bromo-2-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol

[0339] To a solution of 4-bromo-1-iodo-2-methoxybenzene (14.9 g, 47.6 mmol, 1.2 eq.) in THF (100 mL) cooled to -80°C was added at n-BuLi (2.5 M, 19.1 mL, 47.6 mmol, 1.2 eq.) and stirred at for 1 hour under N_2. Then 6-(benzyloxy)-3,4-dihydronaphthalen-1(2H)-one (10 g, 39.6mmol, 1.2 eq.) in THF (30 mL) was added and stirred at -80°C for 3 hours. Once the reaction was completed, the mixture was quenched with H_2O (200 mL) and extracted with EA (400 mL) to give crude product. The residue was purified by column chromatography on silica gel (PE: EA =10: 1) to afford the product 6-(benzyloxy)-1-(4-bromo-2-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (7.3 g, 42%) as an oil.

[0340] LC-MS purity: 100% (UV at 254 nm), 439, 451 $[M+H]^+$.

Step 3: 7-(benzyloxy)-4-(4-bromo-2-methoxyphenyl)-1,2-dihydronaphthalene

[0341] To a mixture of 6-(benzyloxy)-1-(4-bromo-2-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (7 g, 15.98 mmol, 1 eq) in MeOH (70 mL) was added TsOH (60 mg, 0.32 mmol, 0.02 eq) and stirred at 50°C for 0.5 hour. LCMS showed the reaction was completed. The mixture was concentrated to afford 7-(benzyloxy)-4-(4-bromo-2-methoxyphenyl)-1,2-dihydronaphthalene (5.8 g, 86%) as white solid. LC-MS purity: 99.26% (UV at 254 nm), 421, 423 $[M+H]^+$.

Step 4: 1-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-4-(dimethoxymethyl)piperidine

[0342] Ruphos (134.0 mg, 0.286 mmol, 0.2 eq), Ruphos Pd G3 (240.0 mg, 0.286 mmol, 0.2 eq) and t-BuONa (550.0 mg, 5.72 mmol, 4.0 eq) was added to a degassed solution of 7-(benzyloxy)-4-(4-bromo-2-methoxyphenyl)-1,2-dihydronaphthalene (600.0 mg, 1.428 mmol, 1.0 eq) and 4-(dimethoxymethyl)piperidine (340.2 mg, 2.14 mmol, 1.5 eq) in 1,4-dioxane (30 mL). The reaction mixture was heated to 100 °C for 2 hrs. LC-MS showed the reaction was completed. The reaction mixture was cooled to rt, filtered, the precipitate was washed with THF (30 mLx2), the filtrate was evaporated, the residue was purified by SiO_2 column chromatography (EtOAc:PE =1:5) to afford 1-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-4-(dimethoxymethyl)piperidine (530 mg, 74.3%) as a yellow oil. LC-MS purity: 98.3% (UV at 254

nm), 500.1 $[M+H]^+$. ^1H NMR (400M Hz, $CDCl_3$) δ 7.43-7.32 (m, 5H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.69-6.62 (m, 2H), 6.55-6.53 (m, 2H), 5.86 (t, *J* = 4.4 Hz, 1H), 5.03 (s, 2H), 4.10 (d, *J* = 7.6Hz, 1H), 3.75-3.72 (m, 2H), 3.68 (s, 3H), 3.39 (s, 6H), 2.87-2.83 (m, 2H), 2.75-2.68 (m, 2H), 2.42-2.36 (m, 2H), 1.89-1.86 (m, 2H), 1.80-1.75 (m, 1H),1.53-1.43 (m, 2H).

Step 5: 11-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-4-(dimethoxymethyl)piperidine

[0343] To a mixture of 1-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-4-(dimethoxymethyl)piperidine (1.85 g, 3.7 mmol, 1 eq) in DMF (20 mL) was added $PyBr_3$ (1.18 g, 3.7 mmol, 1 eq) in DMF (10 mL) dropwise slowly at 0°C over 30 minutes, then stirred at 0°C for 1 hour. LC-MS showed the reaction was completed. 10 mL of Sat. NH_4Cl solution was added, followed by 110 mL of water, extracted with EtOAc (120 mLx3). The combined organic layers were washed with water (120 mLx2), brine (120 mL), dried over Na_2SO_4, filtered, the filtrate was evaporated. The residue was purified by Chem-flash to afford 1-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-4-(dimethoxymethyl)piperidine (1.51 g, 70.1%) as a yellow solid.

[0344] LC-MS purity: 88.4% (UV at 254 nm), 580.2 $[M+H]^+$.

Step 6: 1-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-4-(dimethoxymethyl)piperidine

[0345] $Pd(dppf)Cl_2$ (227 mg, 0.311 mmol, 0.1 eq), and Na_2CO_3 (660 mg, 6.22mmol, 2.0 eq) was added to a degassed solution of 1-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-4-(dimethoxymethyl)piperidine (1.79 g, 3.11mmol, 1.0 eq) and phenylboronic acid (532 mg, 4.35 mmol, 1.4 eq) in 1,4-dioxane/H_2O (40 mL/4 mL). The reaction mixture was heated to 90 °C for 16 hours. LC-MS showed the reaction was completed. The reaction mixture was cooled to room temperature, filtered, the precipitate was washed with THF (40 mLx2), the filtrate was evaporated , the residue was purified by Chemflash to afford 1-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-4-(dimethoxymethyl)piperidine (1.48 g, 82.8%) as a yellow oil.

[0346] LC-MS purity: 99.4% (UV at 254 nm), 576.1 $[M+H]^+$. ^1H NMR (400M Hz, $CDCl_3$) δ 7.43-7.32 (m, 5H), 7.10-6.99 (m, 5H), 6.83 (d, *J* = 2.4 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.68-6.61 (m, 2H), 6.40-6.37 (m, 2H), 5.05 (s, 2H), 4.08 (d, *J* = 7.6Hz, 1H), 3.68-3.64 (m, 2H), 3.51 (s, 3H), 3.37

(s, 6H), 2.98-2.92 (m, 2H), 2.80-2.76 (m, 2H), 2.68-2.62 (m, 2H), 1.87-1.84 (m, 2H), 1.77-1.73 (m, 1H), 1.51-1.44 (m, 2H).

Step 7: 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

[0347] A mixture of 1-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-4-(dimethoxymethyl)piperidine (1.48 g, 2.57 mmol, 1.0 eq) and Pd/C (700 mg) in MeOH (150 mL) was degassed under reduced pressure, purged with H_2 atmosphere, The reaction mixture was heated to 40 °C for 16 hours. LC-MS showed the reaction was completed. The reaction mixture was cooled to room temperature, filtered, the precipitate was washed with EtOAc (20 mLx2), the filtrate was evaporated, the residue was purified by Chemflash to afford 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (1.12g, 89.4%) as a yellow solid.

[0348] LC-MS purity: 99.4% (UV at 254 nm), 488.3 $[M+H]^+$. ^1H NMR (400M Hz, $CDCl_3$) δ 7.10-7.03 (m, 3H), 6.79-6.76 (m, 3H), 6.65 (s, 1H), 6.51-6.48 (m, 2H), 6.34 (d, J = 8.0 Hz, 1H), 6.10 (s, 1H), 4.77 (d, J = 4.8Hz, 1H) , 4.07 (d, J = 7.2Hz, 1H), 3.60-3.57 (m, 2H), 3.36 (s, 6H), 3.29-3.25 (m, 1H), 3.00-2.97 (m, 5H), 2.59 (t, J = 11.2Hz, 2H), 2.32-2.21 (m, 1H), 1.83-1.80 (m, 2H), 1.73-1.68 (m, 3H), 1.49-1.43 (m, 2H).

Step 8: (5S,6S)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol & (5R,6R)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

[0349] 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (1.12 g, 2.3 mmol) was separated by SFC to afford (5S,6S)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (550 mg) & (5R,6R)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (550 mg).

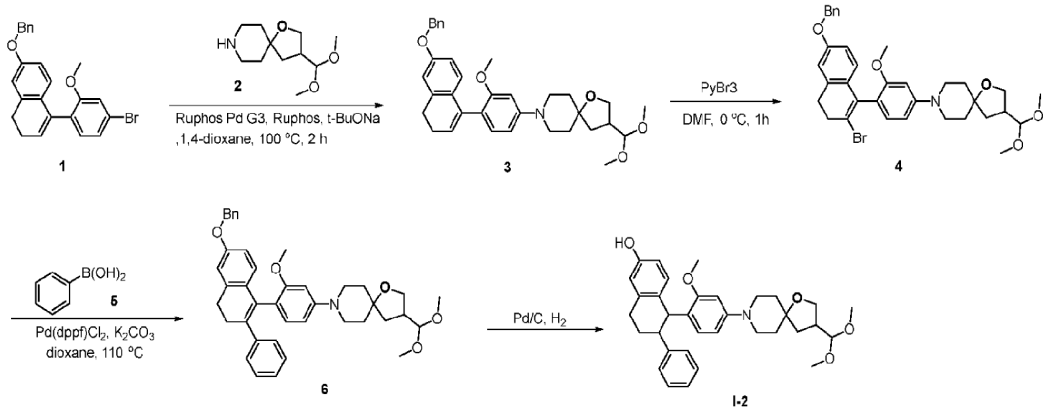
Step 9: 1-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde & 1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde

[0350] A mixture of (5S,6S)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (100 mg) or (5R,6R)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-

ol (100 mg) and formic acid (5 mL) was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure to afford 1-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde & 1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (105 mg, crude) as dark red oil, which was used directly without further purification.

[0351] LC-MS purity: 99.5% (UV at 254 nm), 442.2 $[M+H]^+$.

Intermediate 2: 5-(4-(3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol



Step 2-1:

8-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane

[0352] To a solution of 7-(benzyloxy)-4-(4-bromo-2-methoxyphenyl)-1,2-dihydronaphthalene (1.1 g, 2.61 mmol, 1 eq), 3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (562.1 mg, 2.61 mmol, 1 eq), t-BuONa (752.7 mg, 7.83 mmol, 3.0 eq) and Ruphos (121.6 mg, 0.26 mmol, 0.1 eq) in 1,4-dioxane (20 mL) was added Ruphos Pd G3 (218.2 mg, 0.26 mmol, 0.1 eq) under N_2 atmosphere. The mixture was heated to 100 °C for 2 hrs. LC-MS showed the reaction was completed. The reaction mixture was cooled to rt, filtered, the precipitate was washed with THF (30 mLx2), the filtrate was evaporated, the residue was purified by SiO_2 column chromatography (EtOAc:PE=1:5) to afford 8-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (1.2 g, 82.7%) as a yellow oil.

[0353] LC-MS purity: 100% (UV at 254 nm), LC-MS: 556.2 $[M+H]^+$.

Step 2-2:

8-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane

[0354] To a mixture of 8-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (1.2 g, 2.16 mmol, 1 eq) in DMF (20 mL) was added $PyBr_3$ (686.3 mg, 2.16 mmol, 1 eq) in DMF (10 mL) dropwise slowly at 0°C over 30 minutes, then stirred at 0°C for 1 hour. LC-MS showed the reaction was completed. 10 mL of Sat. NH_4Cl solution was added, followed by 110 mL of water, extracted with EtOAc (120 mLx3). The combined organic layers was washed with water (120 mLx2), brine (120 mL), dried over Na_2SO_4, filtered, the filtrate was evaporated. The residue was purified by Chem-flash to afford 8-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (900 mg, 65.7%) as a yellow solid.

[0355] LC-MS purity: 100% (UV at 254 nm), LC-MS: 634.1, 636.3 $[M+H]^+$.

Step 2-3:

8-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane

[0356] To a solution of compound **1** (900 mg, 1.42 mmol, 1 eq) in dioxane (20 mL) was added compound **2** (207.98 mg, 1.70 mmol, 1.2 eq), H_2O (2 mL), K_2CO_3 (386.73 mg, 2.84 mmol, 2 eq) and $Pd(dppf)Cl_2$ (51.9 mg, 0.07 mmol, 0.05 eq) under N_2 atmosphere. The mixture was heated to 100 °C for 2 hrs. The solution is red and turbid. LC-MS showed the starting material was consumed completely and desired compound was detected. The mixture was concentrated to give a residue. The residue was purified by Chemflash to give 8-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (815 mg, yellow, oil, yield 90.96%). LC-MS purity: 100% (UV at 254 nm), LC-MS: 632.1 $[M+H]^+$.

Step 2-4:

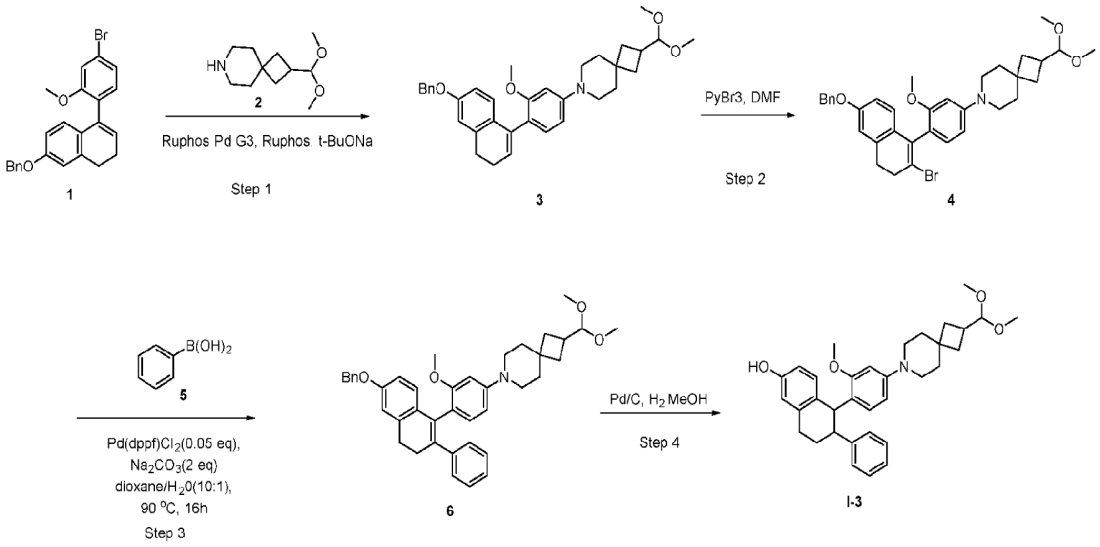
5-(4-(3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

[0357] To a solution of 8-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (815 mg, 1.29 mmol, 1 eq) in MeOH (15 mL) was added Pd/C (82 mg, 0.38 mmol, 0.3 eq) under H_2 (15 Psi) atmosphere. The mixture was heated to 40 °C for 16 hrs. The solution is black and turbid. LC-MS showed the

starting material was consumed completely and desired compound was detected. The mixture was filtered and concentrated to give a residue. The residue was purified by Chemflash to give 5-(4-(3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (640 mg, yellow, oil, yield 91.25%).

[0358] LC-MS purity: 100% (UV at 254 nm), LC-MS: 544.2 $[M+H]^+$

Intermediate 3: 5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol



Step 3-1:

7-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0359] Ruphos (332.0 mg, 0.712 mmol, 0.2 eq), Ruphos Pd G3 (596.0 mg, 0.712 mmol, 0.2 eq) and t-BuONa (1.37 g, 14.2 mmol, 4.0 eq) was added to a degassed solution of 7-(benzyloxy)-4-(4-bromo-2-methoxyphenyl)-1,2-dihydronaphthalene (1.5 g, 3.56 mmol, 1.0 eq) and 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (710.0 mg, 3.56 mmol, 1.0 eq) in 1,4-dioxane (20 mL). The reaction mixture was heated to 100°C and stirred for 16 hrs. LC-MS showed the reaction was completed. The reaction mixture was cooled to rt, the mixture was diluted with water and washed with EA, the organic phase was dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by SiO_2 column chromatography (EtOAc:PE=1:5) to afford 7-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (856 mg, 45%) as a yellow oil.

[0360] LC-MS purity: 100% (UV at 254 nm), MS: 540.3 $[M+H]^+$.

Step 3-2:

7-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0361] To a mixture of 7-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (856 mg, 1.59 mmol, 1 eq) in DMF (20 mL) was added $PyBr_3$ (507.8mg, 1.59 mmol, 1 eq) in DMF (10 mL) dropwise slowly at 0°C over 30 minutes, then stirred at 0°C for 1 hour. LC-MS showed the reaction was completed. 10 mL of Sat. NH_4Cl solution was added, followed by water, extracted with EtOAc. The combined organic layers was washed with water, brine, dried over Na_2SO_4, filtered, the filtrate was evaporated. The residue was purified by Chem-flash to afford 7-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (750 mg, 76%) as a yellow solid.

[0362] LC-MS purity: 100% (UV at 254 nm), MS: 618.2 $[M+H]^+$.

Step 3-3:

7-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0363] $Pd(dppf)Cl_2$ (88.4 mg, 0.121 mmol, 0.1 eq), and Na_2CO_3 (384.7 mg, 3.63mmol, 3.0 eq) was added to a degassed solution of 7-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (750 mg, 1.21mmol, 1.0 eq) and phenylboronic acid (177mg, 1.452 mmol, 1.2 eq) in 1,4-dioxane/H_2O (30 mL/3 mL). The reaction mixture was heated to 90°C for 16 hours. LC-MS showed the reaction was completed. The reaction mixture was cooled to rt, the mixture was diluted with water and washed with EtOAc, the organic phase was dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by SiO_2 column chromatography (EtOAc:PE=1:5) to afford 7-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (605 mg, 81%) as a yellow oil.

[0364] LC-MS purity: 100% (UV at 254 nm), MS: 616.4$[M+H]^+$.

Step 3-4

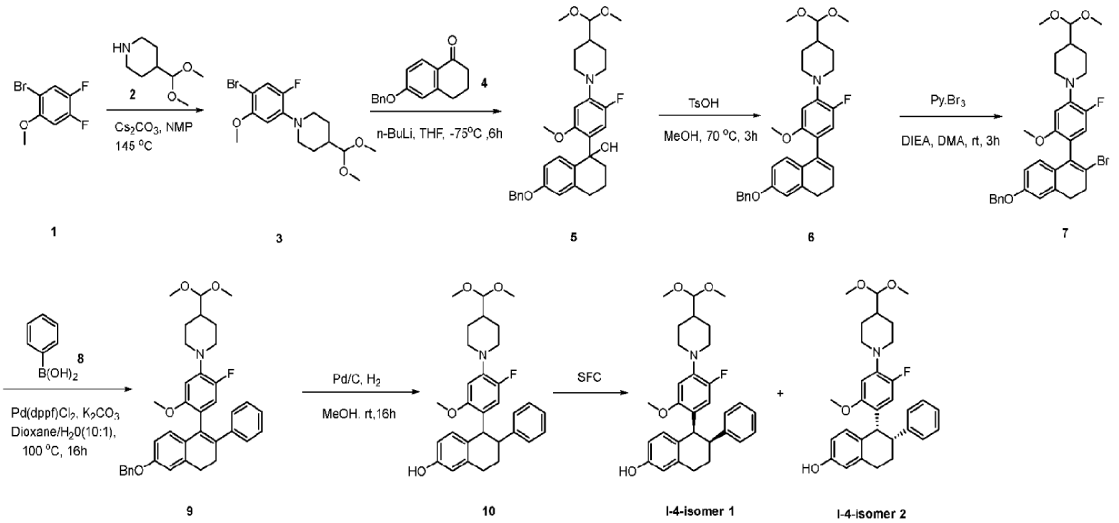
5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

[0365] A mixture of 7-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (605 mg, 0.98 mmol, 1.0 eq) and Pd/C (182 mg) in MeOH (20 mL) was degassed under reduced pressure, purged with H_2 atmosphere, The reaction mixture was heated to 40 °C for 16 hours. LC-MS showed the reaction was completed. The reaction mixture was cooled to room temperature, filtered, the precipitate was washed with MeOH, the filtrate was evaporated , the residue was purified by Chemflash to afford 5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (387.7mg, 74.8%) as a yellow solid.

[0366] LC-MS purity: 100% (UV at 254 nm), LC-MS: 528.4 $[M+H]^+$.

[0367] ^{1}H NMR (400M Hz, DMSO-d6) δ 9.04 (s, 1H), 7.06 (d, *J* = 6.8 Hz, 3H), 6.76 – 6.70 (m, 2H), 6.55 (dd, *J* = 8.1, 5.3 Hz, 2H), 6.44 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.35 (d, *J* = 8.4 Hz, 1H), 6.29 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.10 (s, 1H), 4.64 (d, *J* = 5.1 Hz, 1H), 4.28 (d, *J* = 7.0 Hz, 1H), 3.20 (s, 8H), 2.97 (d, *J* = 4.2 Hz, 2H), 2.93 (s, 3H), 2.89 (dd, *J* = 11.2, 6.0 Hz, 3H), 2.22 – 2.11 (m, 1H), 1.78 (dd, *J* = 11.0, 10.1 Hz, 2H), 1.56 (ddd, *J* = 19.8, 9.2, 2.8 Hz, 8H).

Intermediate 4: 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-5-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (two isomers)



Step 1: 1-(4-bromo-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine

[0368] To a mixture of 1-bromo-4,5-difluoro-2-methoxybenzene (8.5 g, 38.1 mmol, 1 eq.) and 4-(dimethoxymethyl)piperidine (6.1 g, 38.1 mmol, 1 eq.) in NMP (50 mL) was added Cs_2CO_3 (37.3 g, 114 mmol, 3 eq.). The mixture was purged with nitrogen and stirred at 145 °C overnight. The

mixture was cooled to room temperature and then poured into H_2O (500 mL). The mixture was extracted with EtOAc (150 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel eluted with 0-20% EtOAc/hexane to afford 1-(4-bromo-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine as yellow oil. (2.5 g, 18% yield).

[0369] LC-MS purity: 100% (UV at 254 nm), 362.1/364.1 $[M+H]^+$.

Step 2: 6-(benzyloxy)-1-(4-(4-(dimethoxymethyl)piperidin-1-yl)-5-fluoro-2-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol

[0370] To a mixture of 1-(4-bromo-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine (5.0 g, 13.8 mmol, 1 eq.) in dry THF (25 mL) under Argon was added dropwise n-BuLi (2.50 M, 6.6 mL, 1.2 eq.). The mixture was stirred at -75 °C for 1.5h, and 6-(benzyloxy)-3,4-dihydronaphthalen-1(2H)-one (4.2 g, 16.6 mmol, 1.1 eq.) in dry THF (10 mL) was added dropwise. The mixture was stirred at -75 °C for 3h. The mixture was quenched by the addition of the saturated aqueous NH_4Cl. The mixture was poured into H_2O (40 mL) and extracted with EtOAc (2x30 mL). The combined organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluted with 0-30% EtOAc/hexane to afford 6-(benzyloxy)-1-(4-(4-(dimethoxymethyl)piperidin-1-yl)-5-fluoro-2-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (2.0 g, 26.8% yield) as white solid.

[0371] LC-MS purity: 100% (UV at 254 nm), 536.1 $[M+H]^+$.

Step 3: 1-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine

[0372] To a mixture of 6-(benzyloxy)-1-(4-(4-(dimethoxymethyl)piperidin-1-yl)-5-fluoro-2-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (2.5 g, 4.7 mmol, 1 eq.) in MeOH (8 mL) was added TsOH (171 mg, 0.9 mmol, 0.2 eq.). The mixture was stirred at 70°C for 3h and concentrated. The residue was purified by column chromatography on silica gel eluted with 0-30% EtOAc/hexane to afford 1-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine (1.6 g, 65.7% yield) as yellow solid.

[0373] LC-MS purity: 100% (UV at 254 nm), 518.3 $[M+H]^+$.

Step 4: 1-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine

[0374] To a mixture of 1-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine (1.6 g, 3.1 mmol, 1 eq.) and DIEA (0.8 g, 6.2 mmol, 2 eq.) in DMA (10 mL), was added pyridinium tribromide (1.2 g, 3.7 mmol, 1.2 eq.) at 0 °C. The mixture was stirred at room temperature for 3h. The mixture was poured into H_2O (50 mL) and extracted with EtOAc (2x20 mL). The combined organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluted with 0-20% EtOAc/hexane to afford 1-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine (1.6 g, 86.6% yield) as yellow solid.

[0375] LC-MS purity: 100% (UV at 254 nm), 598.2 $[M+H]^+$.

Steps 5: 1-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine

[0376] To a mixture of 1-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine (1.8 g, 3.0 mmol, 1 eq.) in dioxane (16 mL) and H_2O (2 mL), was added phenylboronic acid (522 mg, 4.5 mmol, 1.5 eq.), K_2CO_3 (636 mg, 3 mmol, 2 eq.) followed by $Pd(dppf)Cl_2$ (137 mg, 0.15 mmol, 0.05 eq.). The mixture was stirred at 100 °C for 16 hours under Argon. The mixture was cooled to room temperature, poured into H_2O (50 mL) and extracted with EtOAc (2x20 mL). The combined organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluted with 0-20% EtOAc/hexane to afford 1-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine (1.3 g, 72.2% yield) as yellow solid.

[0377] LC-MS purity: 100% (UV at 254 nm), 594.3 $[M+H]^+$.

Steps 6: 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-5-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

[0378] To a mixture of 1-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-4-(dimethoxymethyl)piperidine (440 mg, 0.7 mmol, 1 eq) in MeOH (10 mL) was added Pd/C (100 mg, 10% on Carbon, wetted with c.a.55% water). The mixture was stirred at room temperature overnight under H_2. The catalyst was removed by filtration and the filtrate was

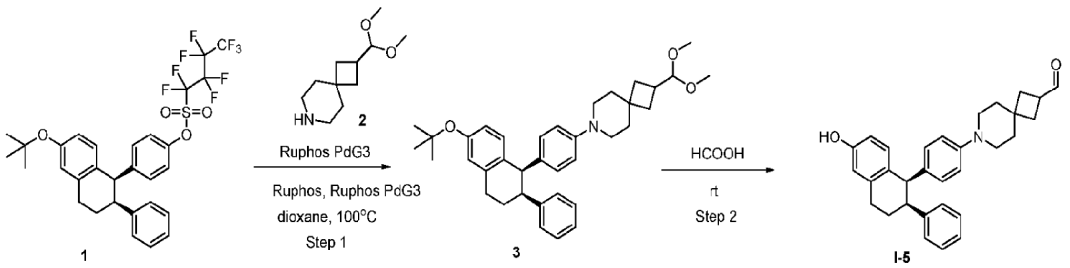
concentrated to afford 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-5-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (200 mg, 53.3% yield) as white solid.

[0379] LC-MS purity: 68.0% (UV at 254 nm), 506.5 $[M+H]^+$.

Steps 7: (5S,6S)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-5-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol & (5R,6R)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-5-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

[0380] 5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-5-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (200 mg, 0.4 mmol) was separated by SFC to afford (5S,6S)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-5-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (90 mg) and (5R,6R)-5-(4-(4-(dimethoxymethyl)piperidin-1-yl)-5-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (90 mg) with both structures being tentatively assigned.

Intermediate 5: 7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde



Step 5-1:

7-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0381] To a mixture of 4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl) phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (100 mg, 0.15 mmol, 1.0 eq), 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (30 mg, 0.15 mmol, 1.0 eq), t-BuONa (44 mg, 0.46 mmol, 3.0eq) and Ruphos (7 mg, 0.02 mmol, 0.1 eq) in 1,4-dioxane (5 mL) was added Ruphos PdG3 (13 mg, 0.02 mmol, 0.1 eq), then stirred at 100 °C for 16 hours. LC-MS showed the reaction was completed. The reaction mixture was cooled to rt, the mixture was diluted with water and washed with EtOAc, the organic phase was dried with Na_2SO_4 and concentrated under vacuum. the residue was purified by SiO_2 column chromatography (EtOAc:PE=1:20) to afford 7-(4-

((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (26 mg, 31%) as a yellow oil.

[0382] LC-MS purity: 62.1% (UV at 254 nm), LC-MS: 554.3 $[M+H]^+$.

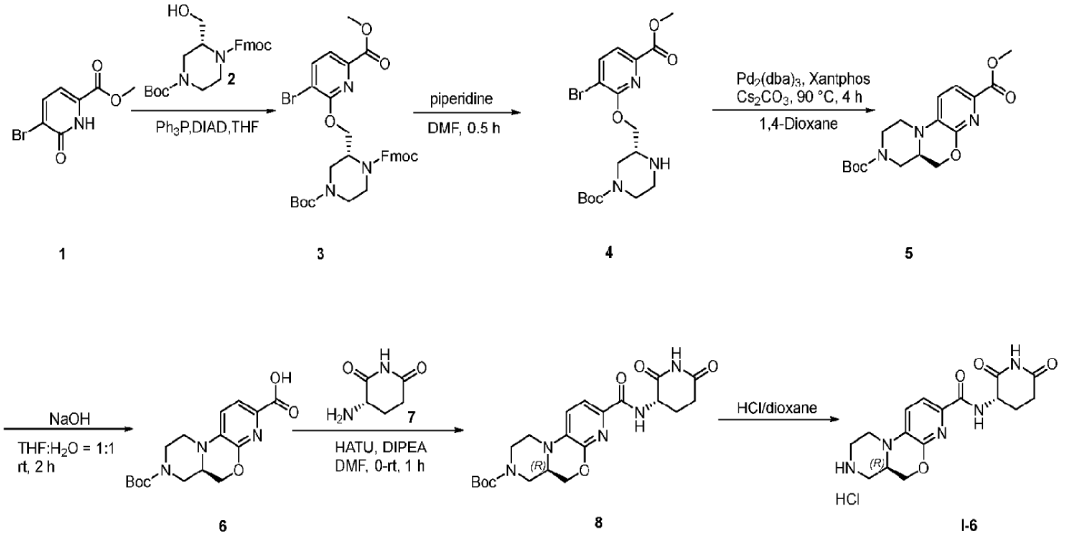
Step 5-2:

7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde

[0383] To a mixture of 7-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (26 mg, 0.04 mmol, 1 eq) in HCOOH (3 mL) was stirred at 25 °C for 16 hours. The mixture was concentrated to give crude product 7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (13 mg, 69%) as a colorless liquid.

[0384] LC-MS purity: 100 % (UV at 254 nm), LC-MS: 452.2 $[M+H]^+$.

Intermediate 6: (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride salt



Step 1: (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate

[0385] To a mixture of methyl 5-bromo-6-oxo-1,6-dihydropyridine-2-carboxylate (2.5 g, 10.7 mmol, 1 eq.) in THF (50 mL) was added (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (5.7 g, 12.9 mmol, 1.2 eq.) and PPh_3 (8.4 g, 32.1

mmol, 3 eq.) and the mixture was stirred at 60 °C. To the mixture was added DIAD (6.5 g, 32.1 mmol, 3 eq.) dropwise and the mixture was stirred at room temperature for 12 h. The mixture was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-30% EtOAc/hexane to afford (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate (5.0 g, 70 % yield) as yellow solid.

Step 2: (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate

[0386] To a mixture of (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate (5 g, 7.6 mmol 1 eq.) in DMF (50 mL) was added piperidine (1.1 g, 15.2 mmol, 2 eq.). The mixture was stirred at room temperature for 1 h, diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic phase was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo*. The crude was purified by column chromatography on silica gel eluted with 0-5% DCM in methanol to give (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate (2.4 g, 75 % yield). LC-MS purity: 100% (UV at 254 nm), ms: 430.2 $[M+1]^+$.

Step 3: (R)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate

[0387] To a mixture of (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate (2.4 g, 5.6 mmol, 1 eq.), XantPhos (486 mg, 0.84 mmol, 0.15 eq.), and Cs_2CO_3(5.4 g, 16.8 mmol, 3 eq.) in dioxane (50 mL) was added $Pd_2(dba)_3$ (511 mg, 0.56 mmol, 0.1 eq.) under Ar flow and the mixture was stirred at 100 °C for 16 h. The mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic phase was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with using 0-50% EtOAc/hexane to give (R)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate (1.3 g, 68 % yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 350.4 $[M+H]^+$.

Step 4: (R)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid

[0388] To a mixture of (R)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate (1.3 g, 3.7 mmol, 1 eq.) in THF (10 mL) and water (10 mL) was added sodium hydroxide (590 mg, 14.8 mmol, 4 eq) and the mixture was stirred at room temperature for 2 h. The mixture was adjusted to pH 5-6 with aq. HCl (1 M) and extracted with ethyl acetate (20 mL). The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was evaporated to afford (R)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid (1.3 g, crude) as white solid. LC-MS purity: 100% (UV at 254 nm), 336.3$[M+H]^+$.

Step 5: tert-butyl (R)-8-(((S)-2,6-dioxopiperidin-3-yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate

[0389] To a mixture of (R)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid (1.3 g, 3.8 mmol, 1 eq) in DMF (10 mL) was added HATU (1.7 g, 4.6 mmol, 1.2 eq) and DIPEA (980 mg, 7.6 mmol, 2 eq) and the mixture was stirred at room temperature for 1 h. The mixture was purified directly by reverse phase column chromatography (0-90% acetonitrile/ 0.05% formic acid)) to afford (R)-tert-butyl 8-(((S)-2,6-dioxopiperidin-3-yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate (1.3 g , 76 % yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 446.2$[M+H]^+$.

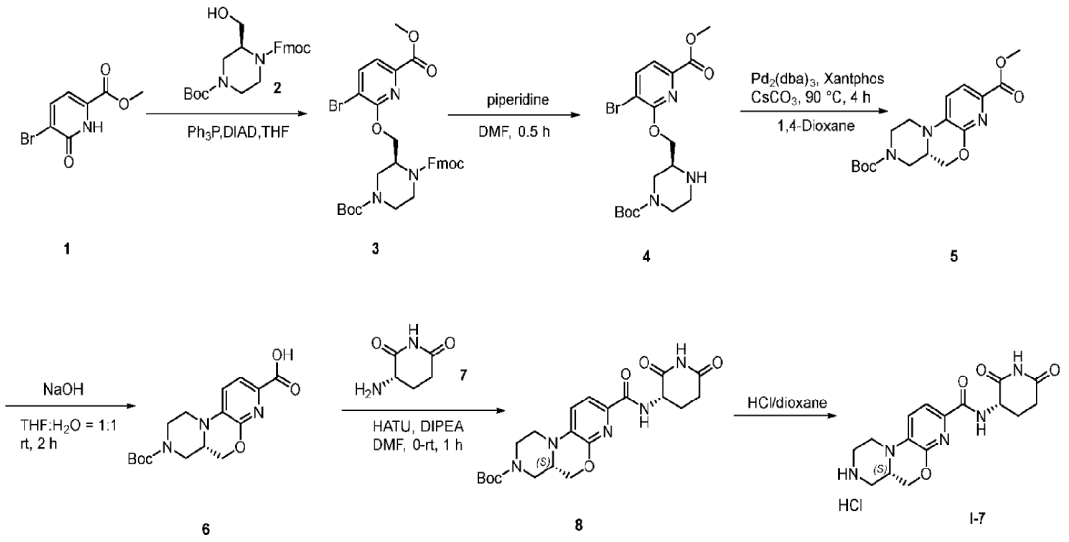
Step 6: (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride

[0390] A mixture of (R)-tert-butyl 8-(((S)-2,6-dioxopiperidin-3-yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate (1.3 g, 2.9 mmol, 1 eq.) in HCl/dioxane (10 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated to afford (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride (1.0 g, 91% yield) as white solid.

[0391] LC-MS purity: 100% (UV at 254 nm), ms: 346.2$[M+1]^+$.

[0392] ^{1}H NMR (400 MHz, DMSO): δ 10.84 (s, 1H), 9.63-9.33 (m, 2H), 8.56 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 4.77-4.70 (m, 1H), 4.51-4.49 (m, 2H), 4.20-4.05 (m, 2H), 3.66-3.55 (m, 1H), 3.47-3.39 (m, 2H), 3.22-2.98 (m, 2H), 2.89-2.67 (m, 2H), 2.26-2.11 (m, 1H), 2.02-1.90 (m, 1H).

Intermediate 7: (S)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride salt



Step 1: (S)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate

[0393] To a mixture of methyl 5-bromo-6-oxo-1,6-dihydropyridine-2-carboxylate (2.5 g, 10.7 mmol, 1 eq.) in THF (50 mL) was added (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (5.7 g, 12.9 mmol, 1.2 eq.) and PPh_3 (8.4 g, 32.1 mmol, 3 eq.) and the mixture was stirred at 60 °C. To the mixture was added DIAD (6.5 g, 32.1 mmol, 3 eq.) dropwise and the mixture was stirred at room temperature for 12 h. The mixture was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-30% EtOAc/hexane to afford (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate (3.0 g, 50 % yield) as yellow solid.

Step 2: tert-butyl (S)-3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate

[0394] To a mixture of (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate (3 g, 5.6 mmol 1 eq.) in DMF (50 mL) was added piperidine (1.1 g, 15.2 mmol, 3 eq.). The mixture was stirred at room temperature for 1 h, diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic phase was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-5%

DCM in methanol to give (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate (2.4 g, 95 % yield). LC-MS purity: 100% (UV at 254 nm), ms: 430.2 $[M+H]^+$.

Step 3: (S)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate

[0395] To a mixture of (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate (2.4 g, 5.6 mmol, 1 eq.), XantPhos (486 mg, 0.84 mmol, 0.15 eq.), and Cs_2CO_3(5.4 g, 16.8 mmol, 3 eq.) in dioxane (50 mL) was added $Pd_2(dba)_3$ (511 mg, 0.56 mmol, 0.1 eq.) under Ar flow and the mixture was stirred at 100 °C for 16 h. The mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic phase was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to give (R)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate (1.3 g, 68 % yield) as white solid. LC-MS purity: 100% (UV at 254 nm), ms: 350.4 $[M+H]^+$.

Step 4: (S)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid

[0396] To a mixture of (R)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate (1.3 g, 3.7 mmol, 1 eq.) in THF (10 mL) and water (10 mL) was added sodium hydroxide (590 mg, 14.8 mmol, 4 eq) and the mixture was stirred at room temperature for 2 h. The mixture was adjusted to pH 5-6 with aq. HCl (1 M) and extracted with ethyl acetate (20 mL). The organic layer was washed with brine, dried over sodium sulfate and filtered. The filtrate was evaporated to afford (R)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid (1.3 g, crude) as white solid. LC-MS purity: 100% (UV at 254 nm), 336.3$[M+H]^+$.

Steps 5: (S)-tert-butyl 8-(((S)-2,6-dioxopiperidin-3-yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate

[0397] To a mixture of (S)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid (880 mg, 2.6 mmol, 1 eq.) in DMF (10 mL) was added T_3P (3.2 mL, 5.2 mmol, 2 eq.) and DIPEA (0.64 mL, 5.2 mmol, 2 eq). The mixture was stirred at room temperature for 1 h, quenched with water (10 mL) and purified directly by reverse

phase column chromatography (0-90%Acetonitrile/ 0.05% Formic acid)) to afford (S)-tert-butyl 8-(((S)-2,6-dioxopiperidin-3-yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate (620 mg, 76 % yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), ms: 446.2 $[M+H]^+$.

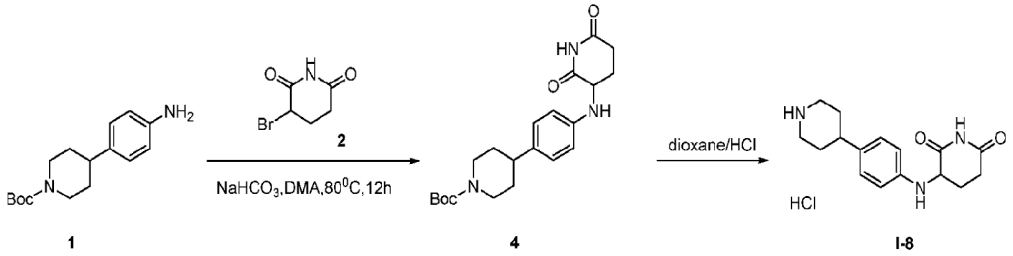
Steps 6: (S)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride

[0398] A mixture of (R)-tert-butyl 8-(((S)-2,6-dioxopiperidin-3-yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate (620 mg, 1.4 mmol, 1 eq.) in HCl/dioxane (10 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated to afford (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride (520 mg, crude) as white solid.

[0399] LC-MS purity: 100% (UV at 254 nm), 346.2$[M+H]^+$.

[0400] ^{1}H NMR (400 MHz, DMSO): δ 10.84 (s, 1H), 9.63-9.33 (m, 2H), 8.56 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 4.77-4.70 (m, 1H), 4.51-4.49 (m, 2H), 4.20-4.05 (m, 2H), 3.66-3.55 (m, 1H), 3.47-3.39 (m, 2H), 3.22-2.98 (m, 2H), 2.89-2.67 (m, 2H), 2.26-2.11 (m, 1H), 2.02-1.90 (m, 1H).

Intermediate 8: 3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt



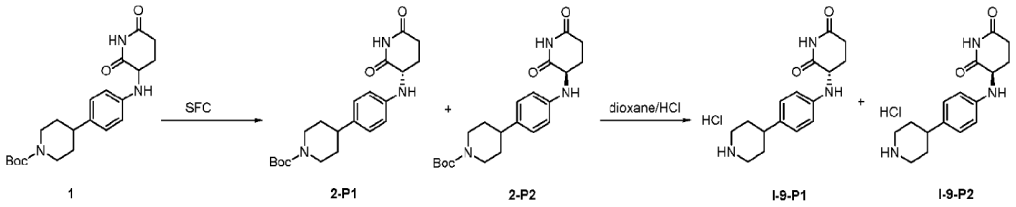
Step 1: tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate

[0401] To a mixture of tert-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (1.5 g, 5.4 mmol 1.0 eq.) in DMA (8 mL) was added 3-bromopiperidine-2,6-dione (1.0 g, 5.428 mmol 1.0 eq) and $NaHCO_3$ (456 mg, 5.4 mmol 1.0 eq.). The mixture was stirred at 80 ° C overnight and cooled to room temperature. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-100% EtOAc/hexane to afford tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate as light blue solid (1.6 g, 76.0 % yield). LC-MS purity: 100% (UV at 254 nm), 388.0 $[M+H]^+$:

Step 2: 3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt

[0402] A mixture of tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate (1.6 g, 4.1 mmol, 1.0 eq.) in HCl/dioxane (10 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford 3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione (1.5 g, crude),. LC-MS purity: 100% (UV at 254 nm), 288.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.11 – 8.76 (m, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.4 Hz, 2H), 4.33 (dd, J = 11.6, 4.8 Hz, 1H), 3.35 – 3.25 (m, 2H), 3.00 – 2.84 (m, 2H), 2.79 – 2.56 (m, 3H), 2.15 – 2.01 (m, 1H), 1.92 – 1.73 (m, 5H).

Intermediate 9: (R or S)-3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt



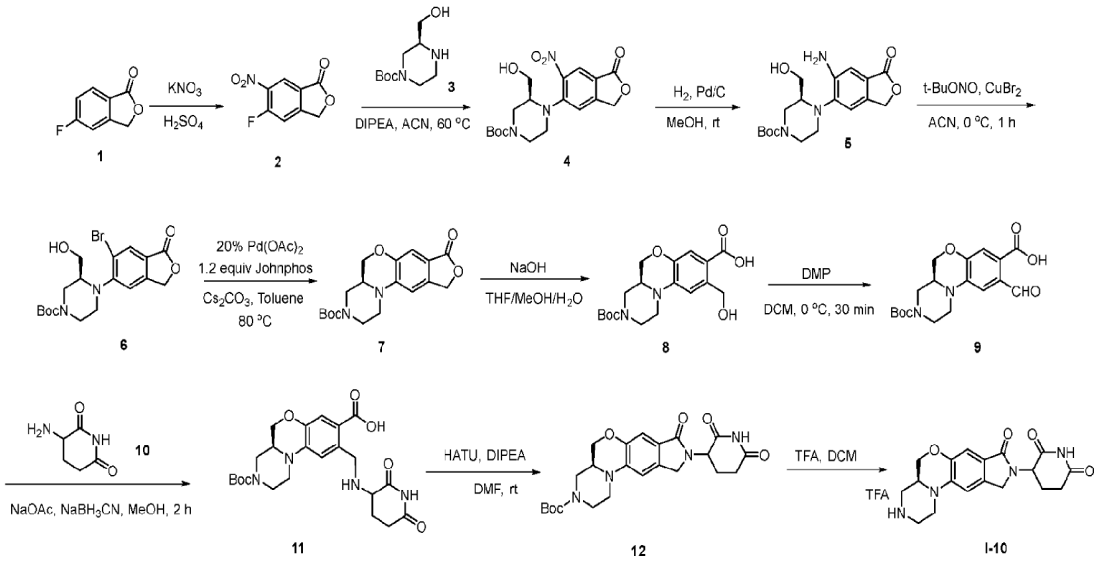
Step 1: (R/S)-tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate

[0403] tert-Butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate (1.9 g, 5 mmol) was purified via SFC to afford (R/S)-tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate (P1:450 mg, P2: 480 mg), LC-MS purity: 100% (UV at 254 nm), 388.0 $[M+H]^+$.

Step 2: (R/S)-3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt

[0404] A mixture of (R/S)-tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate (100 mg, 0.25 mmol, 1.0 eq) in HCl/dioxane (2 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford (R/S)-3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt (90 mg, 100% crude yield),. LC-MS purity: 100% (UV at 254 nm), 288.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.11 – 8.76 (m, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.4 Hz, 2H), 4.33 (dd, J = 11.6, 4.8 Hz, 1H), 3.35 – 3.25 (m, 2H), 3.00 – 2.84 (m, 2H), 2.79 – 2.56 (m, 3H), 2.15 – 2.01 (m, 1H), 1.92 – 1.73 (m, 5H).

Intermediate 10: 3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride salt



Step 1: 5-fluoro-6-nitroisobenzofuran-1(3H)-one

[0405] To a solution of 5-fluoroisobenzofuran-1(3H)-one (10 g, 65.8 mmol, 1.0 eq.) in H_2SO_4 (50 mL) was added KNO_3 (9.97 g, 98.7 mmol, 1.5 eq.) in portions. The reaction mixture was stirred at room temperature for 3 h and slowly poured into ice water. The organic phase was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford 5-fluoro-6-nitroisobenzofuran-1(3H)-one as white solid (10.4 g, 80% yield).

Step 2: tert-butyl (S)-3-(hydroxymethyl)-4-(6-nitro-1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate

[0406] To a solution of 5-fluoro-6-nitroisobenzofuran-1(3H)-one (1 g, 5.0 mmol, 1 eq.) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (1.7 g, 7.5 mmol, 1.5 eq.) in acetonitrile (10 mL) was added DIPEA (2.2 mL, 12.5 mmol, 2.5 eq.) and the mixture was stirred at 60 °C for 6 h. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-5% MeOH/DCM to afford tert-butyl (S)-3-(hydroxymethyl)-4-(6-nitro-1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate as yellow foam (1.3 g, 66% yield).

Step 3: tert-butyl (S)-4-(6-amino-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate

[0407] To a solution of tert-butyl (S)-3-(hydroxymethyl)-4-(6-nitro-1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate (1.0 g, 2.8 mmol, 1 eq.) in MeOH (15 mL) was added Pd/C (300 mg, 10% on carbon, wetted with ca. 55% water). The mixture was degassed and purged with H_2 three times and stirred at room temperature for 4 h. The catalyst was removed by filtration and the filtrate was evaporated to afford tert-butyl (S)-4-(6-amino-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate as light yellow foam (860 mg, 93% yield).

Step 4: tert-butyl (S)-4-(6-bromo-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate

[0408] To a solution of tert-butyl tert-butyl (S)-4-(6-amino-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (468 mg, 1.3 mmol, 1 eq.) in acetonitrile (25 mL) cooled in ice bath was added *t*-BuONO (0.2 mL, 1.7 mmol, 1.3 eq.) and the mixture was stirred for 30 min. Then a solution of $CuBr_2$ (300 mg, 1.3 mmol, 1 eq.) in acetonitrile (6 mL) was added to the solution dropwise and the mixture was stirred at room temperature for 3 h. Then the mixture was diluted with EA (120 mL) and water (120 mL). The organic phase was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-5% MeOH/DCM to afford tert-butyl (S)-4-(6-bromo-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate as brown oil (415 mg, 75% yield).

Step 5: tert-butyl (S)-8-oxo-1,2,4a,5,8,10-hexahydroisobenzofuro[5,6-b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate

[0409] A mixture of tert-butyl (S)-4-(6-bromo-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (140 mg, 0.3 mmol, 1 eq.), $Pd(OAc)_2$ (36.8 mg, 0.15 mmol, 0.5 eq.), JohnPhos (118 mg, 0.36 mmol, 1.2 eq.) and Cs_2CO_3 (214 mg, 0.7 mmol, 2 eq.) in toluene was degassed and purged with N_2 three times, and then the mixture was stirred at 90 °C for 3 h. The mixtures was cooled to room temperature, filtered through Celite, and the filtrate was concentrated. The residue was triturated with MeOH, and the solid was collected by filtration to afford tert-butyl (S)-8-oxo-1,2,4a,5,8,10-hexahydroisobenzofuro[5,6-b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate as yellow solid (90 mg, 80% yield).

Step 6: (S)-3-(tert-butoxycarbonyl)-9-(hydroxymethyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid

[0410] To a solution of tert-butyl (S)-8-oxo-1,2,4a,5,8,10-hexahydroisobenzofuro[5,6-b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (87 mg, 0.25 mmol, 1 eq.) in THF (3 mL) was added a solution of NaOH (60 mg, 1.3 mmol, 6 eq.) in H_2O (1 mL) and the mixture was stirred at 40 °C for 6 h. Then the mixture was concentrated and the residue was diluted with water (4 mL) and acidified to PH 3-4 with 2 N HCl. The mixture was extracted with DCM (10 mL) and the organic phase was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo* to afford (S)-3-(tert-butoxycarbonyl)-9-(hydroxymethyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid as white powder (76 mg , 83% yield).

Step 7: (S)-3-(tert-butoxycarbonyl)-9-formyl-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid

[0411] To a solution of (S)-3-(tert-butoxycarbonyl)-9-(hydroxymethyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid (54 mg, 0.15 mmol, 1 eq.) in DCM (10 mL) cooled at 0 °C was added DMP (93.7 mg, 0.23 mmol, 1.5 eq.) in small portions and the mixture was stirred at 0 °C for 30 min. Then the mixture was diluted with DCM and washed with brine. The organic phase was dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo* to afford (S)-3-(tert-butoxycarbonyl)-9-formyl-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid as yellow solid (50 mg, crude).

Step 7: (4aS)-3-(tert-butoxycarbonyl)-9-(((2,6-dioxopiperidin-3-yl)amino)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid

[0412] To a mixture of (S)-3-(tert-butoxycarbonyl)-9-formyl-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid (70 mg, 0.2 mmol, 1 eq.), 3-aminopiperidine-2,6-dione (47.6 mg, 0.3 mmol, 1.5 eq.) and NaOAc (23.7 mg, 0.3 mmol, 1.5 eq.) dissolved in MeOH (6 mL) was added $NaBH_3CN$ (36 mg, 0.6 mmol, 3 eq.) and the mixture was stirred at room temperature for 1 h. Then the reaction was quenched with water and the mixture was purified by reverse phase column chromatography (0-50%Acetonitrile/ 0.05% formic acid) to afford (4aS)-3-(tert-butoxycarbonyl)-9-(((2,6-dioxopiperidin-3-yl)amino)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid as white powder (35 mg, 38% yield) after lyophilized.

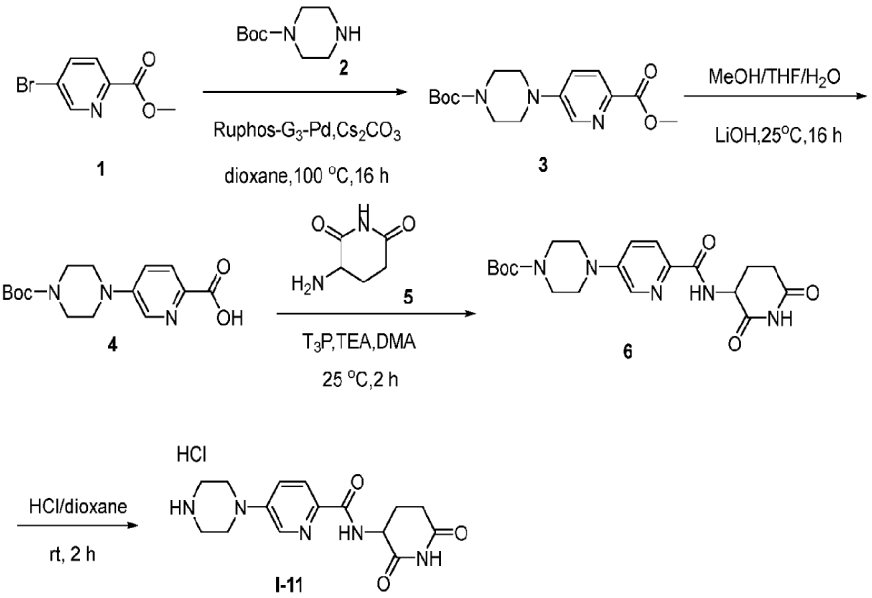
Step 8: tert-butyl (4aS)-9-(2,6-dioxopiperidin-3-yl)-8-oxo-1,2,4a,5,9,10-hexahydro-8H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindole-3(4H)-carboxylate

[0413] To a solution of (4aS)-3-(tert-butoxycarbonyl)-9-(((2,6-dioxopiperidin-3-yl)amino)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid (47 mg, 0.1 mmol, 1 eq.) in DMF (2.5 mL) was added HATU (54 mg, 0.15 mmol, 1.5 eq.) followed by DIPEA (40 mg, 0.3 mmol, 3 eq.) and the mixture was stirred at room temperature for 1 h. Then the reaction was quenched with water and the mixture was purified by reverse phase column chromatography (0-50% acetonitrile/ 0.05% formic acid) to afford tert-butyl (4aS)-9-(2,6-dioxopiperidin-3-yl)-8-oxo-1,2,4a,5,9,10-hexahydro-8H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindole-3(4H)-carboxylate (30 mg, 66% yield) as white powder.

Step 9: 3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride salt trifluoroacetate salt

[0414] A mixture of tert-butyl (4aS)-9-(2,6-dioxopiperidin-3-yl)-8-oxo-1,2,4a,5,9,10-hexahydro-8H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindole-3(4H)-carboxylate (30 mg, 1.0 eq) and HCl/dioxane (2 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford 3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione trifluoroacetate salt as white solid (26 mg, crude). LC-MS: $[M+H]^+$ = 356.90. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.15 (s, 1H), 7.11 (d, J = 5.7 Hz, 1H), 5.13 – 5.02 (m, 1H), 4.41 – 4.27 (m, 3H), 4.20 (d, J = 13.6 Hz, 1H), 4.12 – 4.01 (m, 1H), 3.62 – 3.43 (m, 3H), 3.30 – 3.10 (m, 2H), 3.03 – 2.94 (m, 1H), 2.94 – 2.82 (m, 1H), 2.82 – 2.71 (m, 1H), 2.52 – 2.38 (m, 1H), 2.20 – 2.09 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 174.68, 172.52, 172.49, 171.63, 171.59, 146.42, 146.37, 139.22, 139.20, 138.12, 138.08, 123.85, 123.78, 111.88, 108.70, 108.65, 66.94, 53.72, 53.57, 50.79, 50.75, 48.90, 48.68, 44.36, 44.17, 44.10, 43.63, 43.61, 32.35, 24.08.

Intermediate 11: N-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)picolinamide hydrochloride



Step 1: tert-butyl 4-(6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate

[0415] To a mixture of methyl 5-bromopicolinate (15 g, 69.4 mmol 1 eq.), tert-butyl piperazine-1-carboxylate (12.9 g, 69.4 mmol, 1 eq.) and Cs_2CO_3 (45 g, 139 mmol, 2 eq.) in dioxane (150 mL) was added Ruphos-G3-Pd (2.2 g, 3.5 mmol, 0.05 eq.) under Ar flow. The mixture was stirred at 100 °C for 16 h and cooled to room temperature. The residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford tert-butyl 4-(6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (22 g, crude).

Step 2: 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)picolinic acid

[0416] To a mixture of tert-butyl 4-(6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (22 g, 68.5 mmol, 1 eq.) in MeOH (40 mL)/THF (100 mL)/H_2O (40 mL) was added LiOH (5.5 g, 137 mmol, 2 eq.) and the mixture was stirred at room temperature for 16 h. The mixture was concentrated and the residue was adjusted to pH 6 with 1N HCl. The precipitate was collected by filtration and dried in vacuo to afford 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)picolinic acid (16.3 g, 76.4% yield).

Step 3: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)pyridin-3-yl)piperazine-1-carboxylate

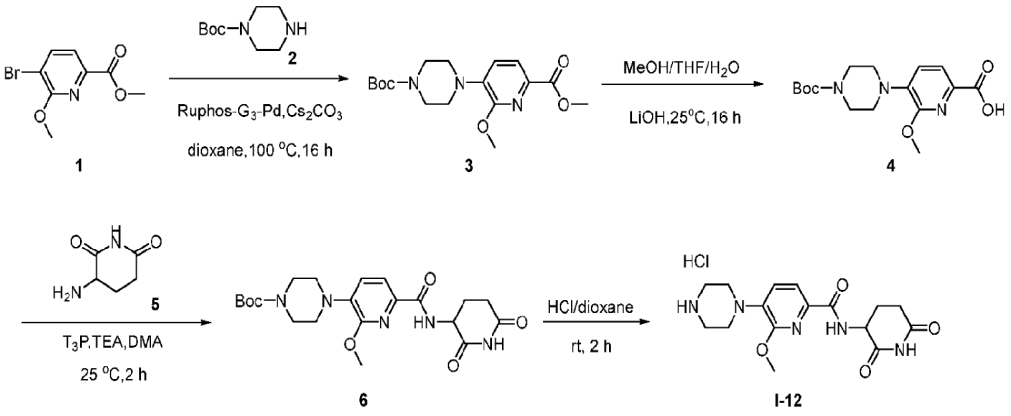
[0417] To a mixture of 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)picolinic acid (1 g, 3.2 mmol, 1 eq.), 3-aminopiperidine-2,6-dione (537 mg, 3.2 mmol, 1 eq.) in DMA (5 ml) was added TEA (0.8 mL, 6.4 mmol, 2 eq.) and T_3P (3 mL, 4.8mmol, 1.5 eq.). The reaction mixture was stirred at room temperature for 2 h, poured into water (50 mL) and extracted with EtOAc (20 mL). The organic

phase was dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-100% EtOAc/hexane to afford tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)pyridin-3-yl)piperazine-1-carboxylate (1.0 g, 78%) as white solid.

Step 4: N-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)picolinamide hydrochloride salt

[0418] A mixture of tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)pyridin-3-yl)piperazine-1-carboxylate (1 g, 2.5 mmol,1.0 eq) in HCl/dioxane (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford N-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)picolinamide hydrochloride salt as white solid (950 mg, crude).

Intermediate 12: N-(2,6-dioxopiperidin-3-yl)-6-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride



Step 1: tert-butyl 4-(2-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate

[0419] To a mixture of methyl 5-bromo-6-methoxypicolinate (900 mg, 3.7 mmol, 1 eq.), tert-butyl piperazine-1-carboxylate (818 mg, 4.4 mmol, 1.2 eq.) and Cs_2CO_3 (1.4 g, 4.4 mmol, 1.2 eq.) in dioxane (15 mL) was added Ruphos-G3-Pd (153 mg, 0.18 mmol, 0.05 eq.) under Ar flow. The mixture was stirred at 100 °C for 16 h and cooled to room temperature. The residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford tert-butyl 4-(2-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (770 mg, 50%).

Step 2: 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-methoxypicolinic acid

[0420] To a mixture of tert-butyl 4-(2-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (70 mg, 0.2 mmol, 1 eq.) in MeOH (1 mL)/THF (1 mL)/H_2O (1 mL) was added LiOH (14 mg, 0.6 mmol, 3 eq.) and the mixture was stirred at room temperature for 16 h. The mixture

was concentrated and the residue was adjusted to pH=6 with 1N HCl. The precipitate was collected by filtration and dried in vacuo to afford 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-methoxypicolinic acid (65 mg, crude).

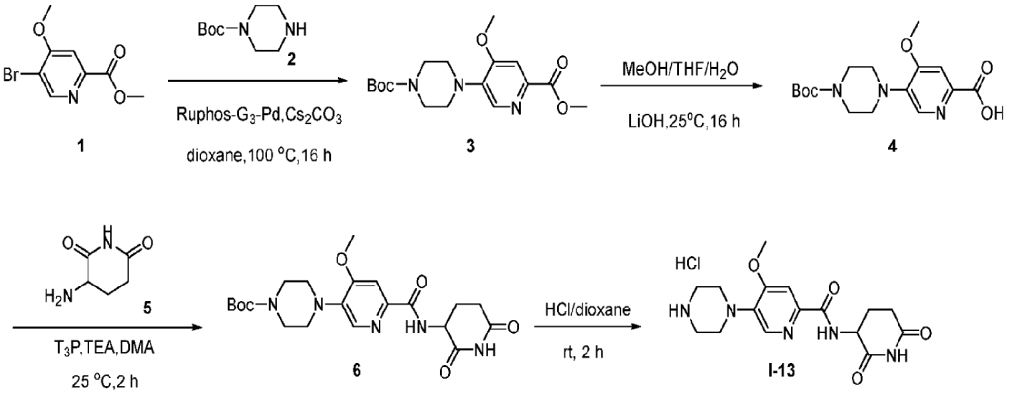
Step 3: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methoxypyridin-3-yl)piperazine-1-carboxylate

[0421] To a mixture of 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-methoxypicolinic acid (80 mg, 0.24 mmol, 1 eq.), 3-aminopiperidine-2,6-dione (46 mg, 0.28 mmol, 1.2 eq.) in DMA (3 ml) was added TEA (48 mg, 0.48 mmol, 2 eq.) and T_3P (152 mg, 0.48 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 2 h, poured into water (30 mL) and extracted with EtOAc (10 mL). The organic phase was dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-100% EtOAc/hexane to afford tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methoxypyridin-3-yl)piperazine-1-carboxylate (101 mg, 97%) as white solid.

Step 4: N-(2,6-dioxopiperidin-3-yl)-6-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride salt

[0422] A mixture of tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methoxypyridin-3-yl)piperazine-1-carboxylate (450 mg, 1 mmol, 1.0 eq.) in HCl/dioxane (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford N-(2,6-dioxopiperidin-3-yl)-6-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride salt as white solid (950 mg, crude).

Intermediate 13: N-(2,6-dioxopiperidin-3-yl)-4-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride salt.



Step 1: tert-butyl 4-(4-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate

[0423] To a mixture of methyl 5-bromo-4-methoxypicolinate (1 g, 4.0 mmol, 1 eq.), tert-butyl piperazine-1-carboxylate (818 mg, 4.4 mmol, 1.2 eq.) and Cs_2CO_3 (1.4 g, 4.4 mmol, 1.2 eq.) in dioxane (15 mL) was added Ruphos-G3-Pd (153 mg, 0.18 mmol, 0.05 eq.) under Ar flow. The mixture was stirred at 100 °C for 16 h and cooled to room temperature. The residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford tert-butyl 4-(4-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (370 mg, 23% yield).

Step 2: 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-methoxypicolinic acid

[0424] To a mixture of tert-butyl 4-(2-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (70 mg, 0.2 mmol, 1 eq.) in MeOH (1 mL)/THF (1 mL)/H_2O (1 mL) was added LiOH (14 mg, 0.6 mmol, 3 eq.) and the mixture was stirred at room temperature for 16 h. The mixture was concentrated and the residue was adjusted to pH=6 with 1N HCl. The precipitate was collected by filtration and dried in vacuo to afford 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-methoxypicolinic acid (65 mg, crude).

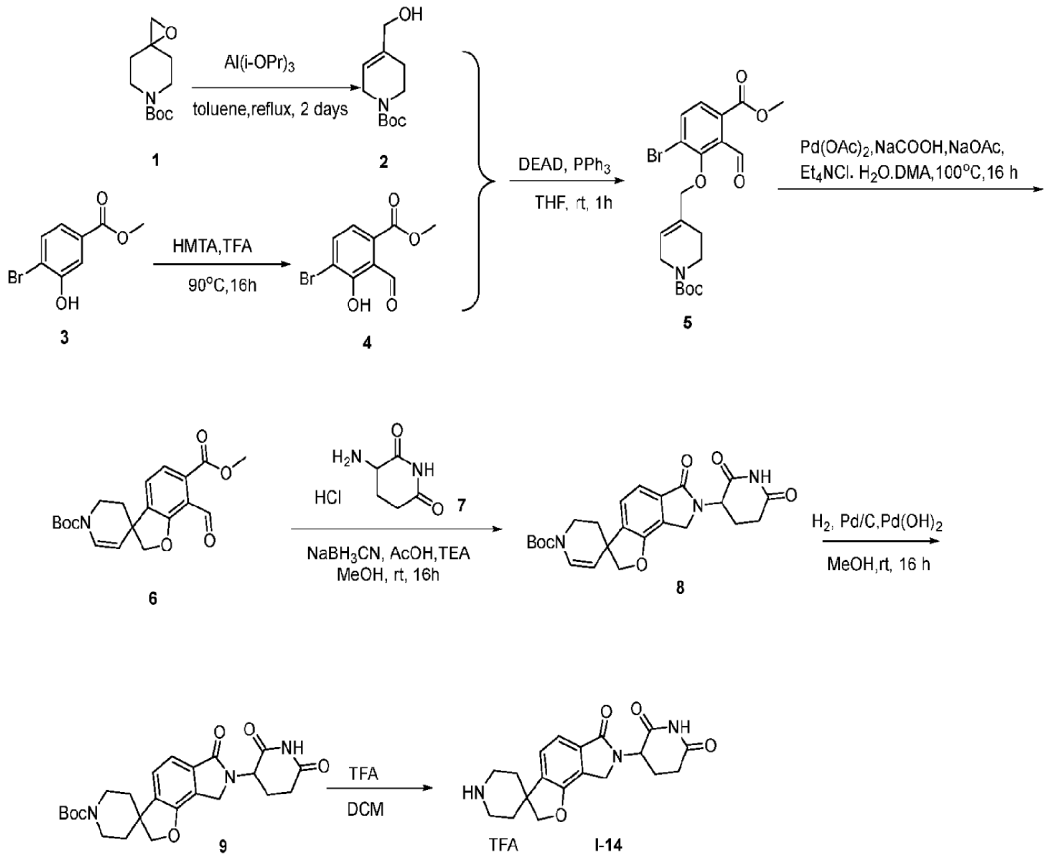
Step 3: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-4-methoxypyridin-3-yl)piperazine-1-carboxylate

[0425] To a mixture of 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-methoxypicolinic acid (160 mg, 0.48 mmol, 1 eq.), 3-aminopiperidine-2,6-dione (92 mg, 0.56 mmol, 1.2 eq.) in DMA (3 ml) was added TEA (97 mg, 0.97 mmol, 2 eq.) and T_3P (152 mg, 0.48 mmol, 1 eq.). The reaction mixture was stirred at room temperature for 2 h, poured into water (30 mL) and extracted with EtOAc (10 mL). The organic phase was dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-100% EtOAc/hexane to afford tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-4-methoxypyridin-3-yl)piperazine-1-carboxylate (97 mg, 95%) as white solid.

Step 4: N-(2,6-dioxopiperidin-3-yl)-4-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride salt

[0426] A mixture of tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-4-methoxypyridin-3-yl)piperazine-1-carboxylate (100 mg,0.22 mmol, 1.0 eq.) in HCl/dioxane (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford N-(2,6-dioxopiperidin-3-yl)-4-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride salt as white solid (90 mg, crude).

Intermediate 14. 3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione trifluoroacetate salt



Step 1: tert-butyl 4-(hydroxymethyl)-3,6-dihydropyridine-1(2H)-carboxylate

[0427] A mixture of the tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate **1** (25 g, 117.4 mmol) and aluminium isopropoxide (35.9 g, 176 mmol) in anhydrous toluene (300 mL) was heated under reflux for 36 h. The reaction was allowed to cool and then poured into aqueous hydrogen chloride (1 M). The aqueous phase was extracted into EA and the organic extracts were dried (Na_2SO_4) then concentrated under reduced pressure. Chromatography of the residue gave the title compound **2** as a colorless oil (12 g, 48%)

Step 2: methyl 4-bromo-2-formyl-3-hydroxybenzoate

[0428] To a solution of methyl 4-bromo-3-hydroxybenzoate 3 (18 g, 77.9 mmol) in TFA (150 mL) was added HMTA (41.5 g, 296 mmol). The solution was stirred at 90°C overnight. 2N HCl was added, and a yellow solid formed. The mixture was stirred for 10 min and then additional 1 L water was added and stirred for 1h. The mixture was filtered. The filter cake was dissolved in DCM and filtered on celite, dried, and then remove most of solvent in vacuo. The result mixture was triturated with MeOH and filtered to afford methyl 4-bromo-2-formyl-3-hydroxybenzoate **4** as a yellow solid (12 g, 59%).

Step 3: tert-butyl 4-((6-bromo-2-formyl-3-(methoxycarbonyl)phenoxy)methyl)-3,6-dihydropyridine-1(2H)-carboxylate

[0429] To a solution of compound **2** (6 g, 23.2 mmol, 1.0 eq.) in dry THF (50 ml), compound **4** (5.9 g, 27.8 mmol, 1.2 eq.) and PPh_3 (7.9 g, 30.1 mmol, 1.3 eq.) was added. The reaction mixture was cooled to 0°C and DIAD (6.6 g, 32.4 mmol, 1.4 eq.) was added dropwise. The resultant mixture was then stirred 1h at room temperature. The solvent was evaporated at reduced pressure and the crude product was purified by silica gel column chromatography using 0-20% EtOAc/hexane. The desired product **5** was obtained as a yellow oil (4 g, 38%).

Step 4: 1'-(tert-butyl) 6-methyl 7-formyl-2',3'-dihydro-1'H,2H-spiro[benzofuran-3,4'-pyridine]-1',6-dicarboxylate

[0430] To a solution of compound **5** (4 g, 8.8 mmol, 1.0 eq.) in DMA (30 mL) was added NaCOOH (0.72 g, 10.6 mmol, 1.2 eq.), $Et_4NCl.H_2O$ (1.95 g, 10.6 mmol, 1.2 eq), $Pd(OAc)_2$ (0.2 g, 0.88 mmol, 0.1 eq) and NaOAc (1.44 g, 17.6 mmol, 2 eq.). The mixture was purged with nitrogen and heated to 100 °C overnight. The mixture was diluted with ethyl acetate and washed with water. The organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by silica gel column chromatography using 0-30% EtOAc/hexane to give compound **6** as a yellow oil (720 mg, yield 24%).

Step 5: tert-butyl 7-(2,6-dioxopiperidin-3-yl)-6-oxo-2',3',7,8-tetrahydro-1'H,2H,6H-spiro[furo[2,3-e]isoindole-3,4'-pyridine]-1'-carboxylate

[0431] To a solution of compound **6** (780 mg, 2.09 mmol, 1 eq.) and compound **6** (344 mg, 2.09 mmol, 1 eq.) in MeOH (10 mL) was added TEA (211 mg, 2.09 mmol, 1 eq.) and AcOH (627 mg, 10.5 mmol, 5 eq.) followed by $NaBH_3CN$ (395 mg, 6.27 mmol, 3 eq.). The mixture was stirred at room temperature for 16 h, diluted with EA, and washed with brine, then dried over sodium sulfate. The solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using 0-100% EtOAc/hexane to give compound **8** as a white solid (400 mg, 42%).

Step 6: tert-butyl 7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

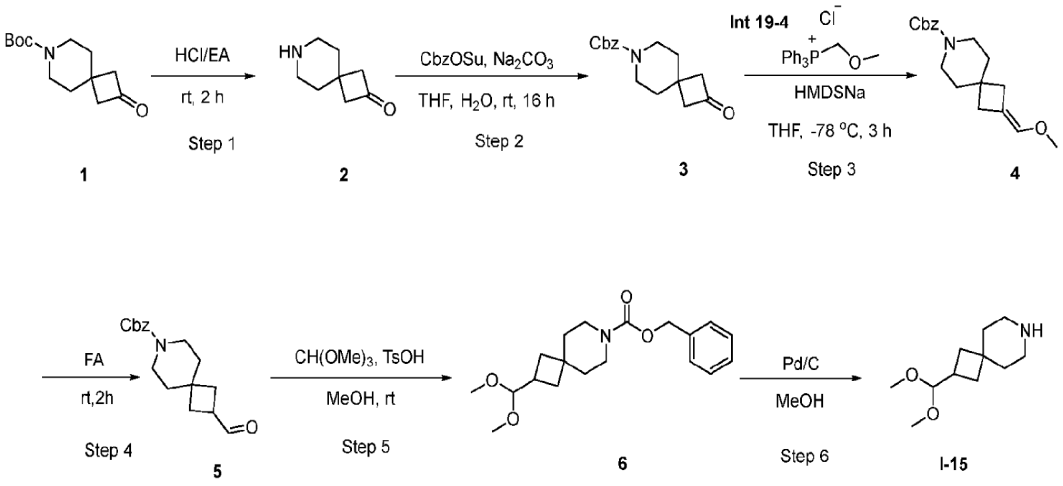
[0432] To a solution of compound **8** (400 mg, 0.88 mmol, 1 eq.) in MeOH was added Pd/C (200 mg, 10% on Carbon, wetted with c.a.55% water) and $Pd(OH)_2$ (200 mg). The mixture was purged with H_2 and stirred at rt overnight under H_2. The mixture was filtered through Celite and the filtrate

was concentrated. The crude product was purified by silica gel chromatography. The desired compound tert-butyl 7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate was obtained as white solid (220mg, 55%). LC/MS (ESI) m/z: 356.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 5.11-5.06 (m, 1H), 4.62-4.57(m, 2H), 4.38 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 3.95 – 3.92 (m, 2H), 2.95 – 2.83 (m, 3H), 2.61 – 2.56 (m, 1H), 2.47 – 2.39 (m, 1H), 1.98 – 1.96 (m, 1H), 1.83-1.77 (m, 2H), 1.71-1.65 (m, 2H), 1.42 (s, 9H).

Step 7: 3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione trifluoroacetate salt

[0433] Compound **9** was treated with TFA in DCM at room temperature to de-protect the N-Boc group to provide intermediate **I-14**. LC/MS (ESI) m/z: 356.15. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.28 (s, 1H), 5.23 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.55 (d, *J* = 1.4 Hz, 2H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.32 (d, *J* = 16.0 Hz, 1H), 4.15 (s, 2H), 3.01 – 2.77 (m, 4H), 2.38 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.29 – 2.17 (m, 1H), 1.92 (t, *J* = 12.5 Hz, 2H), 1.83 – 1.72 (m, 2H).

Intermediate 15: 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane



Step 1: benzyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate

[0434] To a stirred solution of tert-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (24 g, 0.1 mol, 1 eq.) in EA (50 mL) at room temperature was added conc. HCl (45 mL, 0.5 mol, 5 eq.) slowly and the reaction mixture was stirred at rt for 1 hour. Once the reaction was completed, the mixture was diluted with EA (150 mL), poured into Na_2CO_3 suspension (106 g, 1 mol, 10 eq., in

500 mL of water) and the mixture was stirred for 20 min. To the mixture was added CbzOSu (25 g, 0.1 mmol, 1 eq.) and the mixture was stirred for 1 h. The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by silica column chromatography eluting with 50% EA in PE to give compound benzyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (27 g, 0.1 mol, 100%) as a light yellow oil.

Step 2: benzyl 2-(methoxymethylene)-7-azaspiro[3.5]nonane-7-carboxylate

[0435] To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (68 g, 0.2 mol, 2 eq) in dried THF (300 mL) cooled at -70 °C was added NaHMDS (100 mL, 0.2 mol, 2 eq.) dropwise and the mixture was warmed to 0 °C slowly and stirred for 2 h. Then the mixture was cooled at -70 °C and a solution of benzyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (27 g, 0.1 mol, 1eq.) in THF (50 mL) was added. The mixture was warmed to rt slowly and stirred for 2 h. TLC was done to detect the process of the reaction. Once no starting material was left, the mixture was quenched by NH_4Cl solution (500 mL) and diluted with EA (200 mL). The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by silica column chromatography eluting with 30% EA in PE to give compound benzyl 2-(methoxymethylene)-7-azaspiro[3.5]nonane-7-carboxylate (20 g, 0.067 mol, 67%) as a light yellow oil.

Step 3: benzyl 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate

[0436] A solution of benzyl 2-(methoxymethylene)-7-azaspiro[3.5]nonane-7-carboxylate (24 g, 0.67 mol, 1 eq.) in FA (50 mL) was stirred at rt for 4 hours. TLC were done to detect the process of the reaction. Once the reaction was completed, the mixture concentrated and the residue was dissolved in MeOH (120 mL). To the mixture was added $CH(OMe)_3$ (10.6 g, 0.1 mol, 1.5 eq.) followed by $TsOH \cdot H_2O$ (1.5 g, 0.07 mol, 0.1 eq.) and the mixture was stirred at 70 °C for 12 h. TLC were done to detect the process of the reaction. Once the reaction was completed, the mixture was concentrated and the residue was purified by silica column chromatography eluting with 20% EA in PE to give compound benzyl 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (14.6 g, 0.44 mol, 67%) as light yellow oil.

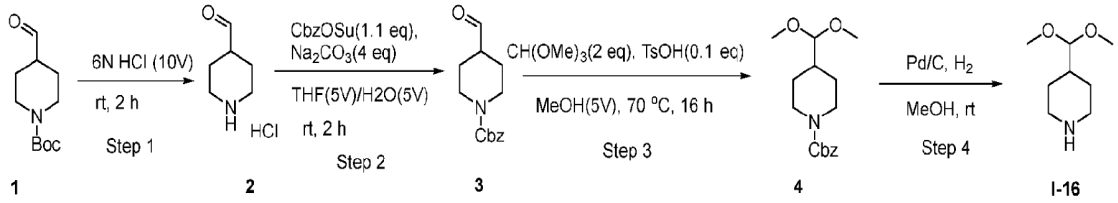
Step 4: 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0437] To a solution of benzyl 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (14.6 g, 0.44 mol, 1 eq.) in MeOH (100 mL) was added Pd/C (4 g, 10% on Carbon, wetted with ca. 55% water) and the mixture was stirred at rt for 12 hours under H_2 (balloon). TLC were done to detect the process of the reaction. Once the reaction was completed, the catalyst was removed by filtration

and the filtrate was concentrated to give compound 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (8.9 g, 0.44 mol, 100%) as a white paste.

[0438] LCMS [M+H]: 200.0. ^{1}H NMR (400 MHz, DMSO-d6) δ 4.57 (d, *J* = 6.8 Hz, 1H), 3.20 (m, 6H), 2.61 (s, 2H), 2.47-2.43 (m, 1H), 1.74 (t, 2H), 1.54-1.44 (m, 4H), 1.34 (t, 2H).

Intermediate 16: 4-(dimethoxymethyl)piperidine



Step 1 and step 2: benzyl 4-formylpiperidine-1-carboxylate

[0439] To a stirred solution of compound tert-butyl 4-formylpiperidine-1-carboxylate (500 g, 2.2 mol, 1 eq.) in EA (500 mL) at room temperature was added conc. HCl (600 mL, 6.6 mol, 3 eq.) slowly and the reaction mixture was stirred at rt for 1 hour. Once the reaction was completed, the mixture was diluted with EA (500 mL), poured into Na_2CO_3 suspension (1160 g, 11 mol, 5 eq., in 3000 mL of water) and the mixture was stirred for 20 min. To the mixture was added CbzOSu (550 g, 2.2 mmol, 1 eq.) and the mixture was stirred for 1 h. The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by silica column chromatography eluting with 50% EA in PE to give compound benzyl 4-formylpiperidine-1-carboxylate (550 g, 2.1 mol, 95%) as a light yellow oil.

Step 3: benzyl 4-(dimethoxymethyl)piperidine-1-carboxylate

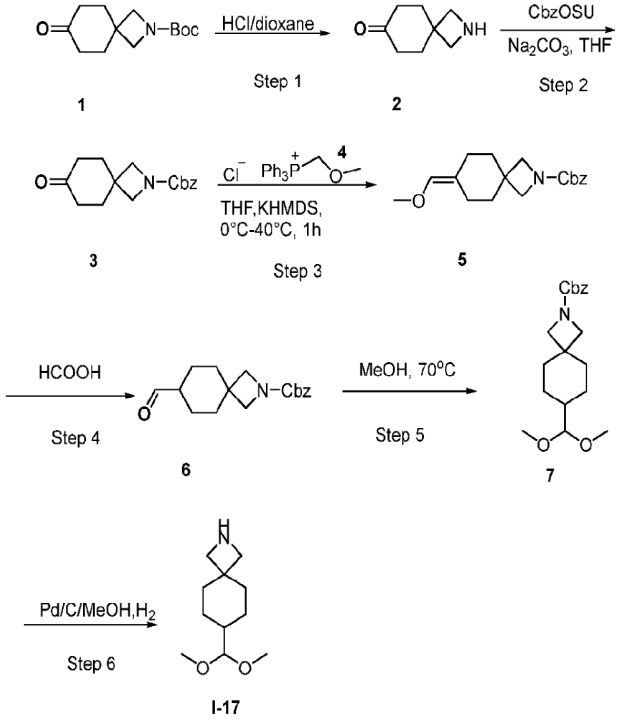
[0440] To a solution of benzyl 4-formylpiperidine-1-carboxylate (150 g, 0.5 mol, 1 eq.) in MeOH (500 mL) was added $CH(OMe)_3$ (212 g, 1 mol, 2 eq.) followed by $TsOH{\cdot}H_2O$ (19 g, 0.1 mol, 0.1 eq.) and the mixture was stirred at 70 °C for 12 h. Once the reaction was completed, the mixture was concentrated and the residue was purified by silica column chromatography eluting with 20% EA in PE to give compound benzyl 4-(dimethoxymethyl)piperidine-1-carboxylate (120 g, 0.41 mol, 82%) as light yellow oil.

Step 4: 4-(dimethoxymethyl)piperidine

[0441] To a solution of compound benzyl 4-(dimethoxymethyl)piperidine-1-carboxylate (120 g, 0.44 mol, 1 eq.) in MeOH (400 mL) was added Pd/C (20 g, 10% on Carbon, wetted with ca. 55% water) and the mixture was stirred at rt for 12 hours under H_2 (balloon). Once the reaction was

completed, the catalyst was removed by filtration and the filtrate was concentrated to give compound 4-(dimethoxymethyl)piperidine (65 g, 0.41 mol, 100%) as a white paste.

Intermediate 17: 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane



Step 1: benzyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate

[0442] To a stirred solution of compound tert-butyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate (2.4 g, 10 mmol, 1 eq.) in EA (5 mL) at room temperature was added conc. HCl (4.5 mL, 50 mol, 5 eq.) slowly and the reaction mixture was stirred at rt for 1 hour. Once the reaction was completed, the mixture was diluted with EA (15 mL), poured into Na_2CO_3 suspension (10.6 g, 0.1 mol, 10 eq., in 50 mL of water) and the mixture was stirred for 20 min. To the mixture was added CbzOSu (2.5 g, 10 mmol, 1 eq.) and the mixture was stirred for 1 h. The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by silica column chromatography eluting with 50% EA in PE to give compound benzyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate (2.7 g, 0.1 mol, 100%) as a light yellow oil.

Step 2: benzyl 7-(methoxymethylene)-2-azaspiro[3.5]nonane-2-carboxylate

[0443] To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (6.8 g, 20 mol, 2 eq) in dried THF (30 mL) cooled at -70 °C was added NaHMDS (10 mL, 20 mol, 2 eq.) dropwise

and the mixture was warmed to 0 °C slowly and stirred for 2 h. Then the mixture was cooled at -70 °C and a solution of benzyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate (2.7 g, 0.1 mol, 1eq.) in THF (5 mL) was added. The mixture was warmed to rt slowly and stirred for 2 h. TLC was done to detect the process of the reaction. Once no starting material was left, the mixture was quenched by NH_4Cl solution (50 mL) and diluted with EA (20 mL). The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by silica column chromatography eluting with 30% EA in PE to give compound benzyl 7-(methoxymethylene)-2-azaspiro[3.5]nonane-2-carboxylate (2.2 g, 7.3 mmol, 73%) as a light yellow oil.

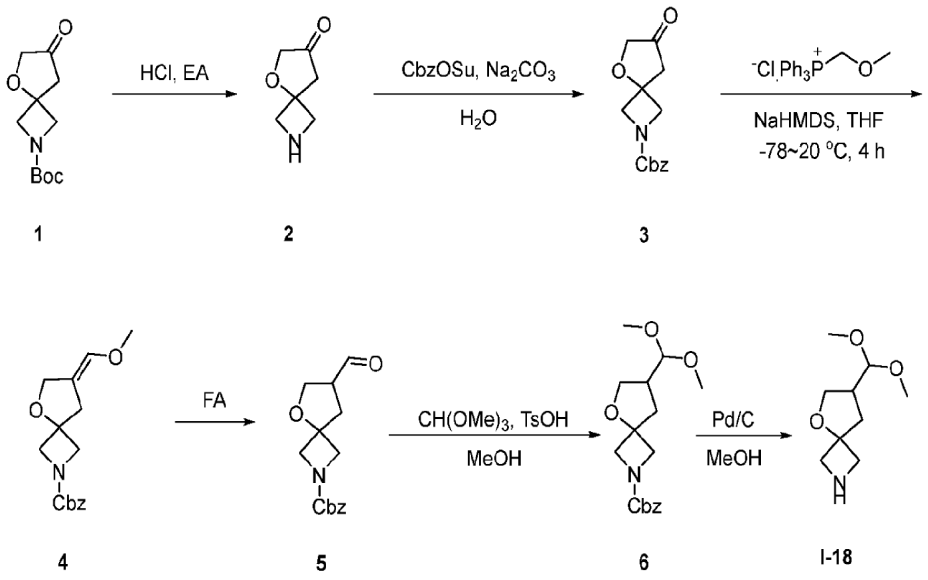
Step 3: benzyl 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate

[0444] A solution of 7-(methoxymethylene)-2-azaspiro[3.5]nonane-2-carboxylate (2.2 g, 7.3 mol, 1 eq.) in FA (5 mL) was stirred at rt for 4 hours. TLC were done to detect the process of the reaction. Once the reaction was completed, the mixture concentrated and the residue was dissolved in MeOH (12 mL). To the mixture was added CH(OMe)3 (1.06 g, 10 mol, 1.5 eq.) followed by $TsOH \cdot H_2O$ (190 mg, 1 mol, 0.1 eq.) and the mixture was stirred at 70 °C for 12 h. TLC were done to detect the process of the reaction. Once the reaction was completed, the mixture was concentrated and the residue was purified by silica column chromatography eluting with 20% EA in PE to give compound benzyl 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate (1.5 g, 4.4 mmol, 67%) as light yellow oil.

Step 4: 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane

[0445] To a solution of compound benzyl 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate (1.5 g, 4.4 mol, 1 eq.) in MeOH (10 mL) was added Pd/C (400 mg, 10% on Carbon, wetted with ca. 55% water) and the mixture was stirred at rt for 12 hours under H_2 (balloon). TLC were done to detect the process of the reaction. Once the reaction was completed, the catalyst was removed by filtration and the filtrate was concentrated to give compound 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane (810 mg, 4 mol, 90%) as a white paste. LCMS: 200 $[M+H]^+$.

Intermediate 18. 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane



Step 1: benzyl 7-oxo-5-oxa-2-azaspiro[3.4]octane-2-carboxylate

[0446] To a stirred solution of tert-butyl 7-oxo-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (10 g, 40 mmol, 1 eq.) in EA (50 mL) at room temperature was added conc. HCl (20 mL, 0.2 mol, 5 eq.) slowly and the reaction mixture was stirred at room temperature for 1 h. Then the mixture was diluted with EA (150 mL), poured into Na_2CO_3 suspension (40 g, 0.4 mol, 10 eq. in 500 mL of water) and the mixture was stirred for 20 min. To the mixture was added CbzOSu (10 g, 40 mmol, 1 eq.) and the mixture was stirred for 1 h. The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 7-oxo-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (10.8 g, 100% yield) as light yellow oil.

Step 2: benzyl (E)-7-(methoxymethylene)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate

[0447] To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (28.3 g, 80 mmol, 2 eq.) in dried THF (300 mL) cooled at -70 °C was added NaHMDS (40 mL, 160 mmol, 2 eq.) dropwise and the mixture was warmed to 0 °C slowly and stirred for 2 h. Then the mixture was cooled at -70 °C and a solution of benzyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (10.8 g, 40 mmol, 1 eq.) in THF (20 mL) was added. The mixture was warmed to room temperature slowly and stirred for 2 h. The mixture was quenched by NH_4Cl solution (200 mL) and diluted with EA (100 mL). The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford

benzyl (E)-7-(methoxymethylene)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (4.5 g, 16 mmol, 40% yield) as light yellow oil.

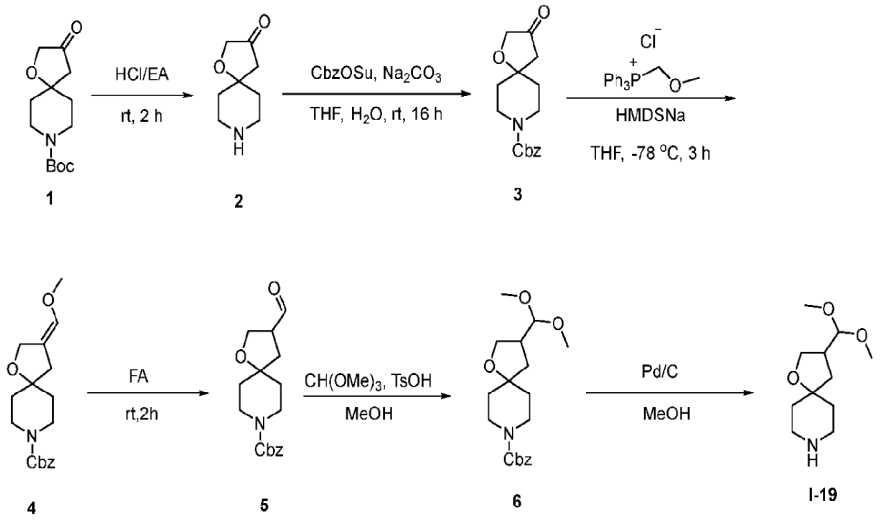
Step 3: benzyl 7-(dimethoxymethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate

[0448] A solution of benzyl (E)-7-(methoxymethylene)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (4.5 g, 16 mmol, 1 eq.) in FA (20 mL) was stirred at room temperature for 4 h. The mixture was concentrated, and the residue was dissolved in MeOH (20 mL). To the mixture was added $CH(OMe)_3$ (2.5 g, 24 mol, 1.5 eq.) followed by $TsOH \cdot H_2O$ (3.1 g, 1.6 mmol, 0.1 eq.) and the mixture was stirred at 70 °C for 12 h. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 7-(dimethoxymethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (2.5 g, 49% yield) as light yellow oil.

Step 4: 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0449] To a solution of benzyl 7-(dimethoxymethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (2.5 g, 7.8 mmol, 1 eq.) in MeOH (20 mL) was added Pd/C (1 g, 10% on carbon, wetted with ca. 55% water) and the mixture was stirred at room temperature for 12 h under H_2 (balloon). The catalyst was removed by filtration and the filtrate was concentrated to afford 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.5 g, crude) as white paste.

Intermediate 19. 3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane



Step 1: benzyl 3-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

[0450] To a stirred solution of tert-butyl 3-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (11 g, 40 mmol, 1 eq.) in EA (50 mL) at room temperature was added conc. HCl (20 mL, 0.2 mol, 5 eq.) slowly and the reaction mixture was stirred at room temperature for 1 h. Then the mixture was diluted with EA (150 mL), poured into Na_2CO_3 suspension (40 g, 0.4 mol, 10 eq. in 500 mL of water) and the mixture was stirred for 20 min. To the mixture was added CbzOSu (10 g, 40 mmol, 1 eq.) and the mixture was stirred for 1 h. The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 7-oxo-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (11 g, 95% yield) as light yellow oil.

Step 2: benzyl (Z)-3-(methoxymethylene)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

[0451] To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (28.3 g, 80 mmol, 2 eq.) in dried THF (300 mL) cooled at -70 °C was added NaHMDS (40 mL, 160 mmol, 2 eq.) dropwise and the mixture was warmed to 0 °C slowly and stirred for 2 h. Then the mixture was cooled at -70 °C and a solution of benzyl 3-oxo-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (11 g, 40 mmol, 1 eq.) in THF (20 mL) was added. The mixture was warmed to room temperature slowly and stirred for 2 h. The mixture was quenched by NH_4Cl solution (200 mL) and diluted with EA (100 mL). The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl (Z)-3-(methoxymethylene)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (5.4 g, 17 mmol, 44% yield) as light yellow oil.

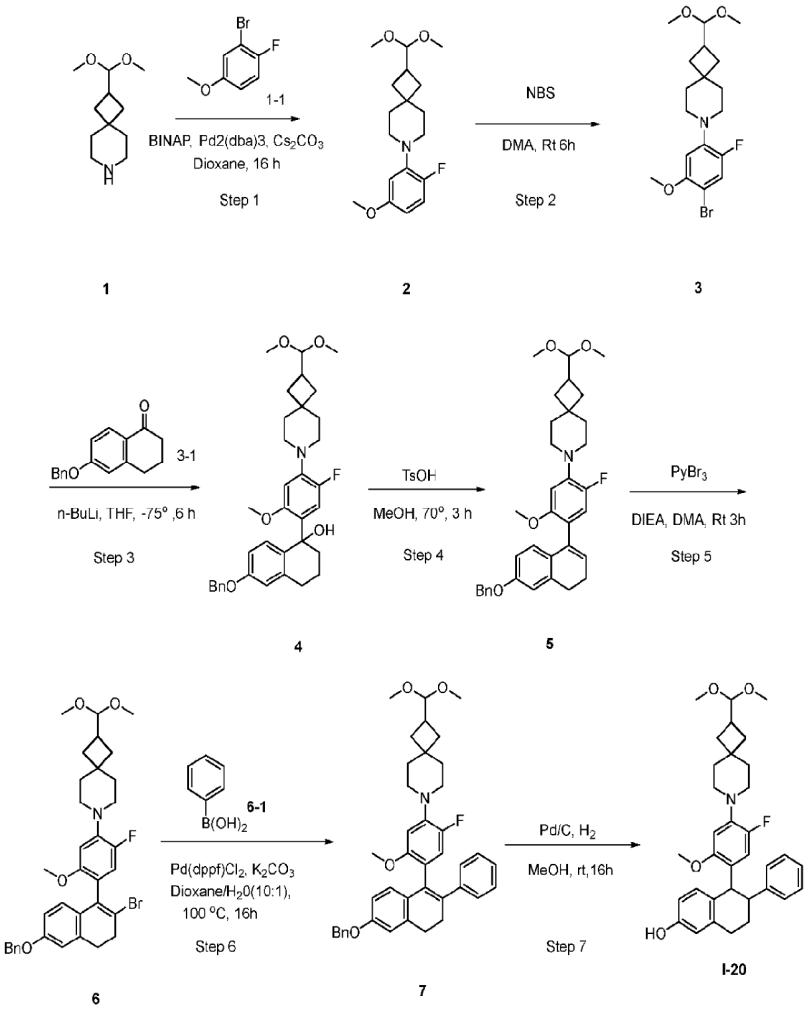
Step 3: benzyl 3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate

[0452] A solution of benzyl (E)-7-(methoxymethylene)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (5.4 g, 17 mmol, 1 eq.) in FA (20 mL) was stirred at room temperature for 4 h. The mixture was concentrated, and the residue was dissolved in MeOH (20 mL). To the mixture was added $CH(OMe)_3$ (2.5 g, 24 mol, 1.5 eq.) followed by $TsOH \cdot H_2O$ (3.1 g, 1.6 mmol, 0.1 eq.) and the mixture was stirred at 70 °C for 12 h. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (3.2 g, 50% yield) as light yellow oil.

Step 4: 3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane

[0453] To a solution of benzyl 7-(dimethoxymethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (3.5 g, 10 mmol, 1 eq.) in MeOH (30 mL) was added Pd/C (1 g, 10% on Carbon, wetted with ca. 55% water) and the mixture was stirred at room temperature for 12 h under H2 (balloon). The catalyst was removed by filtration and the filtrate was concentrated to afford 3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (2.1 g, crude) as white paste.

Intermediate 20. 5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol



Step 1: 2-(dimethoxymethyl)-7-(2-fluoro-5-meth2-(dimethoxymethyl)-7-(2-fluoro-5-methoxyphenyl)-7-azaspiro[3.5]nonaneoxyphenyl)-7-azaspiro[3.5]nonane

[0454] To a mixture of 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (10.0 g, 50.18 mmol, 1 eq.), 2-bromo-1-fluoro-4-methoxybenzene (11.0 g, 55.19 mmol, 0.1 eq.) and Cs_2CO_3 (32.7 g, 100.35

mmol, 2 eq.) in dioxane (60 ml) were added BINAP (3.12 g, 5.02 mmol, 0.1 eq.) and $Pd_2(dba)_3$ (4.59 g, 5.02 mmol, 0.1 eq.). The whole mixture was stirred at 100 °C for 16 hours under Ar. Once finished, the mixture was cooled to room temperature followed by dilution with ethyl acetate (150 mL). The mixture was washed with water (100 mL). The organic layers were collected, washed with brine (2 x 100 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel eluted with 0-40 % EtOAc/hexane to afford 2-(dimethoxymethyl)-7-(2-fluoro-5-methoxyphenyl)-7-azaspiro[3.5]nonane (10.20 g, 62.86% yield) as yellow oil.

[0455] LC-MS purity: 100% (UV at 254 nm), 324.5 $[M+H]^+$

Step 2: 7-(4-bromo-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0456] To a mixture of 2-(dimethoxymethyl)-7-(2-fluoro-5-methoxyphenyl)-7-azaspiro[3.5]nonane (10.20 g, 31.54 mmol, 1.0 eq.) in DMA (50 ml) was added N-bromosuccinimide (6.74 g, 37.85 mmol, 1.2 eq.) at 10 °C. The whole mixture was then stirred at room temperature for 6 hours. Once finished, the mixture was diluted with ethyl acetate (150 mL) and washed with water (200 mL). The organic layer was collected, washed with brine (2 x 100 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel eluted with 0-45 % EtOAc/hexane to afford 7-(4-bromo-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (10.00 g, 78.81% yield) as yellow solid.

[0457] LC-MS purity: 97.2% (UV at 254 nm), 402.2 $[M+H]^+$.

Step 3: 6-(benzyloxy)-1-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol

[0458] To a mixture of 7-(4-bromo-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (2.70 g, 6.71 mmol, 1 eq) in dry THF (10 mL) under Argon was added dropwise n-BuLi (2.50 M, 3.22 mL, 1.2 eq). The mixture was stirred at -78°C for 1.5 h followed by the dropwise addition of 6-(benzyloxy)-3,4-dihydronaphthalen-1(2H)-one (1.86 g, 7.38 mmol, 1.1 eq) in dry THF (10 mL). The mixture was then stirred at -78°C for 3 h. Once TLC (PE:EA= 5:1) showed the starting material was consumed completely, the mixture was quenched by the addition of the saturated aqueous NH_4Cl at 0 °C. The mixture was poured into H_2O (40 mL), extracted with EtOAc (30.0 mLx2), and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by silica gel

column chromatography using 0-40% EtOAc/hexane to afford 6-(benzyloxy)-1-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (1.30 g, 33.65% yield) as a white solid.

[0459] LC-MS purity: 96.2% (UV at 254 nm), 575.3 $[M+H]^+$.

Step 4: 7-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0460] To a mixture of 6-(benzyloxy)-1-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (1.30 g, 2.26 mmol, 1.00 eq) in MeOH (8 mL) was added TsOH (7.78 mg, 0.05 mmol, 0.02 eq). The mixture was stirred at 75°C for 2 min. Once TLC (PE:EA=5:1) showed the starting material was consumed completely, the mixture was concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-20% EtOAc/hexane to afford 7-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.20 g, 98.29% yield) as a yellow solid.

[0461] LC-MS purity: 96.2% (UV at 254 nm), 558.3 $[M+H]^+$.

Step 5: 7-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0462] To a mixture of 7-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.20 g, 2.15 mmol, 1.00 eq) and DIEA (0.56 g, 4.30 mmol, 2.00 eq) in DMA (10 mL), was added pyridinium tribromide (0.83 g, 2.58 mmol, 1.2 eq) at 0° C. The mixture was stirred at 25° C for 2 h. Once LC-MS showed the starting material was consumed completely, the mixture was poured into H_2O. The mixture was then extracted with EtOAc (3 x 50 mL), and the organic layer was washed with brine (3 x 50 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography using 0-20% EtOAc/hexane to afford 7-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.00 g, 73.01% yield) as a yellow solid.

[0463] LC-MS purity: 95.6% (UV at 254 nm), 637.2 $[M+H]^+$.

Steps 6: 7-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

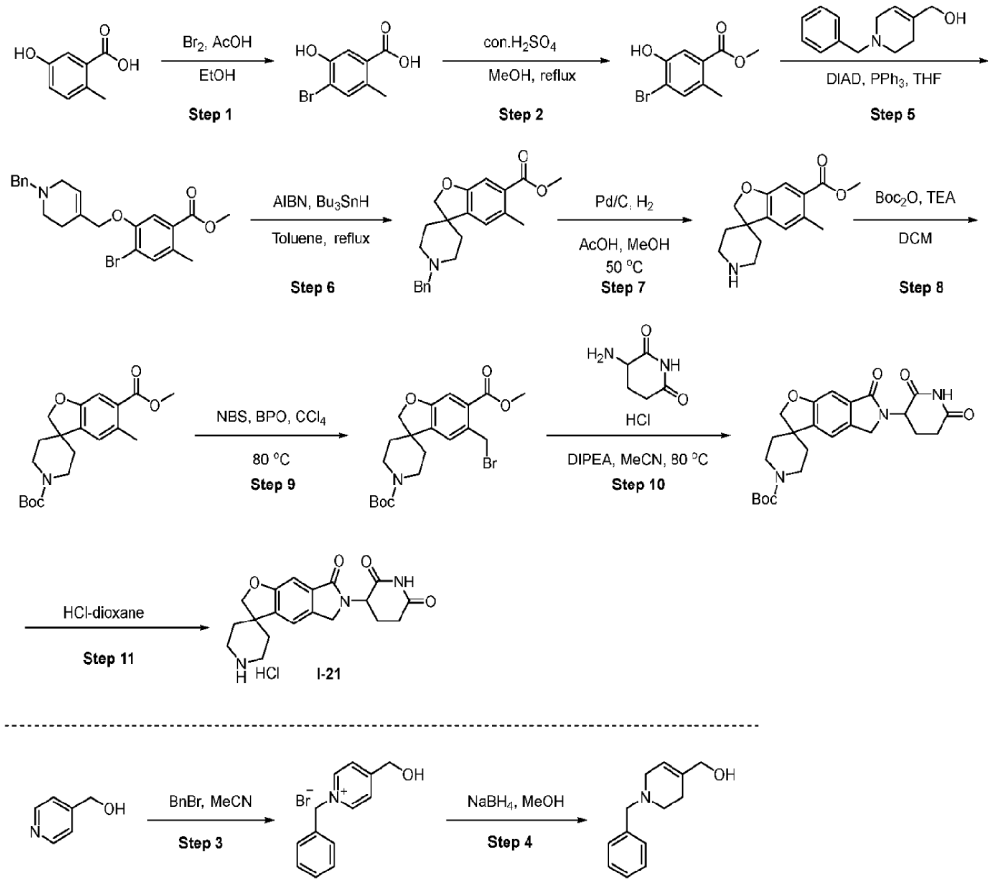
[0464] To a mixture of 7-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.00 g, 1.57 mmol, 1.00 eq) in dioxane (16 mL) and H_2O (2 mL), were added phenylboronic acid (0.23 g, 1.89 mmol, 1.2 eq), K_2CO_3 (0.43 g, 3.14 mmol, 2.00 eq) and $Pd(dppf)Cl_2$ (0.11 g, 0.16 mmol, 0.1 eq). The mixture was stirred at 90°C for 12 hours under Argon. Once LC-MS showed the starting material was consumed completely, the mixture was poured into H_2O, and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-30% EtOAc/hexane to afford 7-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (0.95 g, 95.42% yield) as a yellow solid. LC-MS purity: 98.0% (UV at 254 nm), 634.3 $[M+H]^+$.

Steps 7: 5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

[0465] To a mixture of 7-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (0.70 g, 1.5 mmol, 1.00 eq) in MeOH (10 mL) was added Pd/C (100 mg, 10% on crbon, wetted with c.a.55% water). The whole mixture was then stirred at room temperature overnight under H_2. Once the reaction finished, Pd/C was filtered, and the filtrate was concentrated in vacuum to afford 5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (0.70 g, 85.58% yield) as a white solid.

[0466] LC-MS purity: 97.2% (UV at 254 nm), 546.5 $[M+H]^+$.

Intermediate 21. 3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione hydrochloride



Step 1: 4-bromo-5-hydroxy-2-methylbenzoic acid.

[0467] To a solution of 5-hydroxy-2-methylbenzoic acid (5.0 g, 32.9 mmol, 1.0 eq) in a mixture of ethanol (20 mL) and acetic acid (10 mL) was added dropwise bromine (3.4 mL, 65.7 mmol, 2.0 eq.). The reaction mixture was stirred for 10 h at room temperature, quenched with aqueous sodium thiosulfate solution (50 mL), and concentrated. The aqueous layer was extracted with ethyl acetate (50 mL x 3). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to get crude 4-bromo-5-hydroxy-2-methylbenzoic acid (7.6 g, yield 100%) as a white solid. The crude product was directly used in next step without further purification. LC-MS (ESI): mass calcd. for $C_8H_7BrO_3$, 229.96; m/z found, 231.2 $[M+H]^+$.

Step 2: methyl 4-bromo-5-hydroxy-2-methylbenzoate

[0468] Con. H_2SO_4 (12 mL) was added to a suspension of 4-bromo-5-hydroxy-2-methylbenzoic acid (15 g, 65.72 mmol) in methanol (100 mL). The mixture was refluxed for 16 h. After evaporation, the residue was diluted with water (100 mL) and extracted with EA (100 mL x 3). The organic layer was washed with H_2O (100 mL x 2), saturated aqueous $NaHCO_3$ solution (100

mL x 2) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue purified by flash column chromatography on silica gel (PE/EA = 4/1) to afford methyl 4-bromo-5-hydroxy-2-methylbenzoate (7.5 g, yield 47%) as a colorless solid. LC-MS (ESI): mass calcd. for $C_9H_9BrO_3$, 243.97; m/z found, 245.2 $[M+H]^+$.

[0469] ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.36 (s, 1H), 5.52 (s, 1H), 3.88 (s, 3H), 2.50 (s, 3H).

Step 3: 1-benzyl-4-(hydroxymethyl)pyridin-1-ium bromide

[0470] To a solution of (pyridin-4-yl)methanol (8.9 g, 81.6 mmol, 1.0 eq) in CH_3CN (80 mL) was added a solution of (bromomethyl)benzene (11.705 mL, 97.9 mmol, 1.2 eq) in CH_3CN (40 mL). The reaction mixture was refluxed stirred at 90 °C for 3 h. After evaporation, the residue was washed with methyl tert-butyl ether, filtered, and dried to afford 1-benzyl-4-(hydroxymethyl)pyridin-1-ium bromide (16.33 g, yield 100%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{13}H_{14}NO$, 200.11; m/z found, 200.3 $[M]^+$.

Step 4: (1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methanol

[0471] To a solution of 1-benzyl-4-(hydroxymethyl)pyridin-1-ium bromide (16.3 g, 81.4 mmol, 1.0 eq) in CH_3OH (150 mL) was added $NaBH_4$ (9.3 g, 244.2 mmol, 3.0 eq) in portions at -20 °C. The mixture was stirred at -20 °C for 1 h. The reaction was quenched with brine (100 mL) and extracted with EtOAc (200 mL x 3). The organic layer was washed with brine (100 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH_3OH in DCM, from 0% to 10%) to afford (1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methanol (15 g, yield 91%) as a red oil. LC-MS (ESI): mass calcd. for $C_{13}H_{17}NO$, 203.13; m/z found, 204.4 $[M+H]^+$.

[0472] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 - 7.18 (m, 4H), 7.16 - 7.12 (m, 1H), 5.43 (s, 1H), 4.61 (s, 1H), 3.71 (s, 2H), 3.42 (s, 2H), 2.76 (s, 2H), 2.39 (t, J = 5.6 Hz, 2H), 1.91 (s, 2H).

Step 5: methyl 5-[(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methoxy]-4-bromo-2-methylbenzoate

[0473] To a solution of methyl 4-bromo-5-hydroxy-2-methylbenzoate (200 mg, 0.82 mmol, 1.0 eq), (1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methanol (166 mg, 0.82 mmol, 1.0 eq), and PPh_3 (321 mg, 1.22 mmol, 1.5 eq) in dry THF (10 mL) was added dropwise DIAD (0.25 mL, 1.22 mmol. 1.5 eq) at 0 °C under the N_2 atmosphere. The solution was stirred for 2 h. After evaporation, the residue was purified by flash column chromatography on silica gel (PE/EA = 2/1 to 1/1) to afford methyl 5-[(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methoxy]-4-bromo-2-methylbenzoate

(300 mg, yield 85%) as a white solid. LC-MS (ESI): mass calcd. for $C_{22}H_{24}BrNO_3$, 429.09; m/z found, 431.30 $[M+H]^+$.

Step 6: methyl 1'-(cyclohexylmethyl)-5-methyl-2H-spiro[1-benzofuran-3,4'-piperidine]-6-carboxylate

[0474] Tributyl tin hydride (0.5 mL, 1.84 mmol, 4.0 equiv) was added to a solution of methyl 5-[(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methoxy]-4-bromo-2-methylbenzoate (200 mg, 0.46 mmol, 1.0 eq) and AIBN (15 mg, 0.09 mmol, 0.2 eq) in toluene (10 mL). The solution was refluxed in a sealed tube for 6 h. After cooled down to room temperature, The solution was quenched with saturated potassium fluoride solution (40 mL) and stirred at room temperature for 0.5 h. The mixture was extracted with EA (40 mL x 3). The organic layer was washed brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (EA/PE = 1/1) to afford methyl 1'-(cyclohexylmethyl)-5-methyl-2H-spiro[1-benzofuran-3,4'-piperidine]-6-carboxylate (20 mg, yield 43%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{22}H_{25}NO_3$, 351.18; m/z found, 352.30 $[M+H]^+$.

[0475] ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.27 (m, 6H), 6.99 (s, 1H), 4.37 (s, 2H), 3.85 (s, 3H), 3.54 (s, 2H), 2.89 (d, J = 10.2 Hz, 2H), 2.52 (s, 3H), 2.10 - 1.95 (m, 4H), 1.70 (d, J = 11.4 Hz, 2H).

Step 7: methyl 5-methyl-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylate

[0476] A mixture of methyl 1'-benzyl-5-methyl-2H-spiro[1-benzofuran-3,4'-piperidine]-6-carboxylate (1.0 g, 2.845 mmol, 1.0 eq), acetic acid (1 mL, 5.7 mmol, 6.1 eq), and 10% Pd/C (200 mg) in MeOH (20 mL) was stirred at 50 °C under H_2 (1 atm) for 3 h. After filtration, the filtrate was concentrated to get methyl 5-methyl-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylate (970 mg, yield 100%) as a colorless oil, which was directly used in the next step without further purification. LC-MS (ESI): mass calcd. for $C_{15}H_{19}NO_3$, 261.14; m/z found, 262.40 $(M+H)^+$.

Step 8: 1'-(tert-butyl) 6-methyl 5-methyl-2H-spiro[benzofuran-3,4'-piperidine]-1',6-dicarboxylate

[0477] To a stirred solution of methyl 5-methyl-2H-spiro[1-benzofuran-3,4'-piperidine]-6-carboxylate (970 mg, 3.7 mmol, 1.0 eq) and TEA (1 mL, 7.4 mmol, 2.0 eq) in DCM (10 mL) was added dropwise Boc_2O (0.8 mL, 3.7 mmol, 2.0 eq) at 0 °C. The mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water (10 mL) and extracted with DCM (30 mL x 2). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 1'-(tert-butyl) 6-methyl 5-methyl-2H-spiro[benzofuran-3,4'-piperidine]-1',6-

dicarboxylate (1.28 g, yield 100%) as a white soild. LC-MS (ESI): mass calcd. for $C_{20}H_{27}NO_5$, 361.19; m/z found, 306.4 $[M+H-56]^+$.

Step 9: 1'-(tert-butyl) 6-methyl 5-(bromomethyl)-2H-spiro[benzofuran-3,4'-piperidine]-1',6-dicarboxylate

[0478] A mixture of methyl 1'-benzyl-5-methyl-2H-spiro[1-benzofuran-3,4'-piperidine]-6-carboxylate (220 mg, 0.609 mmol, 1 eq), NBS (130 mg, 0.73 mmol, 1.2 eq), and BPO (60 mg, 0.243 mmol, 0.4 eq) in CCl_4 (10 mL) was refluxed for 4 h. After cooled to room temperature, the mixture was filtered, then the filtration was concentrated and to give 1'-*tert*-butyl 6-methyl 5-(bromomethyl)-2H-spiro[1-benzofuran-3,4'-piperidine]-1',6-dicarboxylate (100 mg, yield 37%) as a light-yellow solid. LC-MS (ESI): mass calcd. for $C_{20}H_{26}BrNO_5$, 439.10; m/z found, 462.20, $[M+Na]^+$.

Step 10: tert-butyl 6-(2,6-dioxopiperidin-3-yl)-7-oxo-6,7-dihydro-2H,5H-spiro[furo[2,3-f]isoindole-3,4'-piperidine]-1'-carboxylate

[0479] DIPEA (0.12 mL, 0.681 mmol, 3.0 eq) was added to 1'-tert-butyl 6-methyl 5-(bromomethyl)-2H-spiro[1-benzofuran-3,4'-piperidine]-1',6-dicarboxylate (100 mg, 0.227 mmol, 1.0 eq) and 3-aminopiperidine-2,6-dione hydrochloride (56 mg, 0.341 mmol, 1.5 eq) in MeCN (5 mL) under nitrogen. The resulting suspension was stirred at 80 °C for 24 h. The reaction mixture was cooled to room temperature and filtered. The solid was washed with MeCN and purified by prep-TLC (100% EtOAc) to afford tert-butyl 6-(2,6-dioxopiperidin-3-yl)-7-oxo-6,7-dihydro-2H,5H-spiro[furo[2,3-f]isoindole-3,4'-piperidine]-1'-carboxylate (50 mg, yield 48%) as a white solid. LC-MS (ESI): mass calcd. for $C_{24}H_{29}N_3O_6$, 455.51; m/z found, 456.50, $(M+H)^+$.

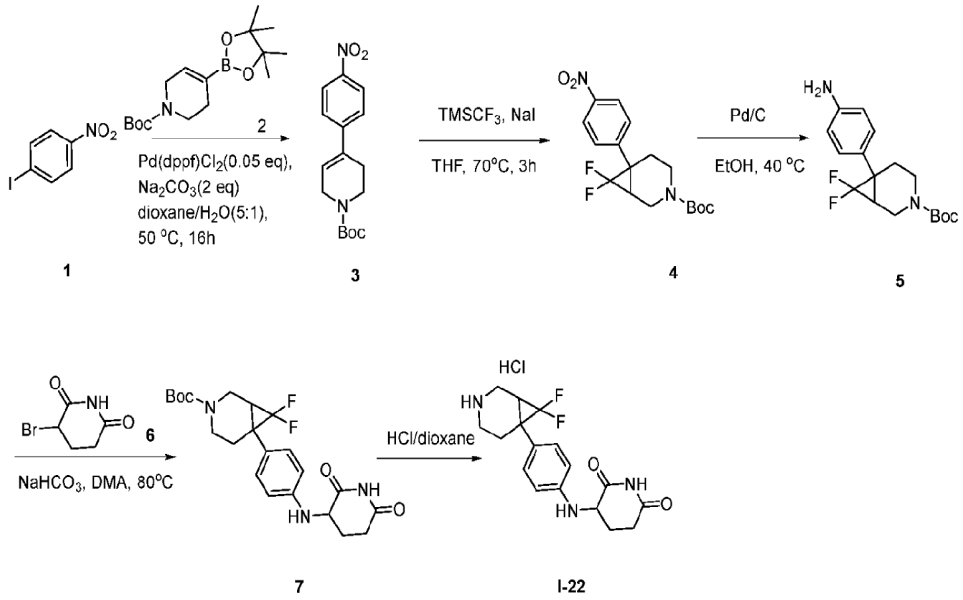
Step 11: 3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

[0480] To a solution of tert-butyl 6-(2,6-dioxopiperidin-3-yl)-7-oxo-2,5,6,7-tetrahydrospiro[furo[2,3-f]isoindole-3,4'-piperidine]-1'-carboxylate (50 mg, 0.11 mmol, 1.0 eq) in DCM (1 mL) was added HCl-dioxane solution (4 *M*, 1 mL, 4 mmol, 36 eq) and the mixture was stirred for 30 min. After evaporation, the residue was purified by prep-HPLC with YMC-TA C18 (5 um, 20 x 250 mm), and mobile phase of 5-95% ACN in water over 10 min, and then hold at 100% ACN for 2 min, at a flow rate of 25 mL/min to get 3-{7-oxo-2,5,6,7-tetrahydrospiro[furo[2,3-f]isoindole-3,4'-piperidine]-6-yl}piperidine-2,6-dione hydrochloride (30

mg, yield 70%) as a white solid._LC-MS (ESI): mass calcd. for $C_{19}H_{21}N_3O_4$, 355.19; m/z found, 356.20 $[M+H]^+$.

[0481] ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.78 (s, 2H), 7.36 (s, 1H), 7.06 (s, 1H), 5.11 - 5.06 (m, 1H), 4.58 (s, 2H), 4.38 (d, J = 17.0 Hz, 1H), 4.25 (d, J = 17.0 Hz, 1H), 3.30 - 3.27 (m, 2H), 3.04 - 2.92 (m, 2H), 2.93 - 2.84 (m, 1H), 2.62 - 2.56 (m, 1H), 2.44 - 2.29 (m, 1H), 2.09 - 1.97 (m, 3H), 1.90 - 1.79 (m, 2H).

Intermediate 22. 3-((4-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt



Step 1: tert-butyl 4-(4-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate

[0482] To a mixture of 1-iodo-4-nitrobenzene (10 g, 40.1 mmol 1 eq.) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (14.9 g, 48.2 mmol, 1.2 eq.) in dioxane (100 mL)/H_2O (20 ml) was added Pd(pddf)Cl_2 (1.9 g, 2.0 mmol, 0.05 eq.) and Na_2CO_3 (12.8 g, 120.5 mmol, 3 eq.) under Ar. The reaction mixture was stirred at 50 °C under N_2 for 16 h. The mixture was concentrated and purified by column chromatography on silica gel eluted with 0-20% EtOAc/hexane to afford tert-butyl 4-(4-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (6.7 g, 54% yield) as white solid.

Step 2: tert-butyl 7,7-difluoro-6-(4-nitrophenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate

[0483] To a mixture of tert-butyl 4-(4-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (600 mg, 2 mmol 1 eq.) and NaI (14.9 g, 48.2 mmol, 1.2 eq.) in THF (10 mL) was added Pd(pddf)Cl_2

(150 mg, 1 mmol, 0.5 eq.) followed by $TMSCF_3$ (1.4 g, 10 mmol, 5 eq.). The reaction mixture was stirred at 70 °C under N_2 for 3 h. The mixture was concentrated and purified by column chromatography on silica gel eluted with 0-20% EtOAc/hexane to afford tert-butyl 7,7-difluoro-6-(4-nitrophenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (700 mg, crude) as brown oil.

Step 3: tert-butyl 6-(4-aminophenyl)-7,7-difluoro-3-azabicyclo[4.1.0]heptane-3-carboxylate

[0484] To a mixture of tert-butyl 7,7-difluoro-6-(4-nitrophenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (400 mg, 1.1 mmol, 1 eq.) in EtOH (10mL) was added Pd/C (100 mg). The reaction mixture was stirred at 40 °C for 16 h under H_2. The catalyst was removed by filtration and the filtrate was concentrated to afford tert-butyl 6-(4-aminophenyl)-7,7-difluoro-3-azabicyclo[4.1.0]heptane-3-carboxylate (360 mg, crude) as yellow oil.

[0485] LC-MS purity: 98.1% (UV at 254 nm),269.1 $[M+H-56]^+$.

Step 4: tert-butyl 6-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)-7,7-difluoro-3-azabicyclo[4.1.0]heptane-3-carboxylate

[0486] To a mixture of tert-butyl 6-(4-aminophenyl)-7,7-difluoro-3-azabicyclo[4.1.0]heptane-3-carboxylate (970 mg, 3 mmol 1.0 eq.) in DMA (8 mL) was added 3-bromopiperidine-2,6-dione (570 mg, 3 mmol 1.0 eq.) and $NaHCO_3$ (251 mg, 3 mmol, 1.0 eq.). The mixture was stirred at 80 ° C overnight and cooled to room temperature. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-100% EtOAc/hexane to afford tert-butyl 6-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)-7,7-difluoro-3-azabicyclo[4.1.0]heptane-3-carboxylate as yellow solid (1 g, 65 % yield).

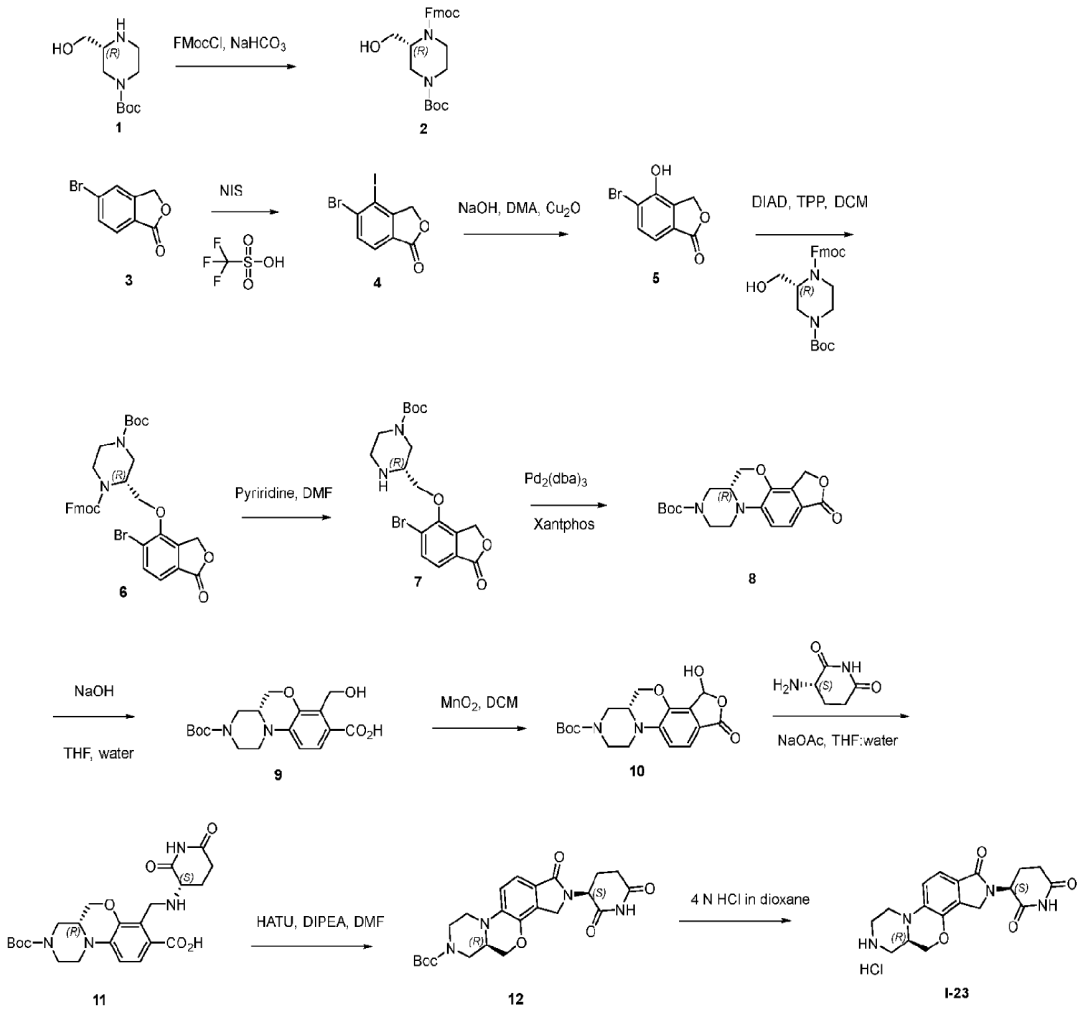
[0487] LC-MS purity: 100% (UV at 254 nm), 436.0 $[M+H]^+$.

Step 5: 3-((4-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt

[0488] A mixture of tert-butyl 6-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)-7,7-difluoro-3-azabicyclo[4.1.0]heptane-3-carboxylate (40 mg, 1.0 eq) in HCl/dioxane (2 mL) was stirred at 20 °C for 2 h. The after reaction was direct concentration as to give 3-((4-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt as white solid (40 mg, crude).

[0489] LC-MS purity: 100% (UV at 254 nm), 336.1 $[M+H]^+$.

[0490] Intermediate 23: (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride salt



Step 1: 1-((9H-fluoren-9-yl)methyl) 4-(tert-butyl) (R)-2-(hydroxymethyl)piperazine-1,4-dicarboxylate

[0491] (*R*)-1-Boc-3-(Hydroxymethyl)piperazine (**1**, 10 g, 46.2 mmol) was dissolved in a mixture of DCM (180 mL) and sat. $NaHCO_3$ (180 mL). FMocCl (46.2 mmol) was dissolved in DCM (15 mL) and added dropwise with vigorous stirring. The mixture was stirred for 1 hour. The layers were separated and the aqueous phase was extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo to give an oil. The crude product was purified by silica gel column chromatography using 0-80% EtOAc/hexane (80% yield).

Step 2: 5-bromo-4-iodoisobenzofuran-1(3H)-one:

[0492] To a solution of 5-Bromo-3H-isobenzofuran-1-one (**3**, 5 g, 23.4 mmol, 1 eq.) in trifluoromethanesulfonic acid (68 g, 40 mL, 19.30 eq) was added NIS (5.5 g, 24.6 mmol, 1.05 eq.) at 0 °C in portions. The mixture was allowed to warm to room temperature and stirred overnight. TLC (hexane: ethyl acetate = 5:1) showed no starting material remained and two new spots (R_f = 0.4, 0.5) formed. The reaction mixture was poured into ice-water (100 mL) and yellow solid precipitated. The mixture was filtered and the filter cake was washed with ice cold water. The filter cake was dissolved in DCM (500 mL) and washed with 1 (M) $Na_2S_2O_3$ followed by dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated to afford a yellow solid. The crude product was purified on a 120 g silica column running a 0-10% EtOAc/hexane gradient over 70 min. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.83 (d, J= 8.0 Hz, 1H), 7.77 (d, J= 8.0 Hz, 1H), 5.10 (s, 2H).

Step 3: 5-bromo-4-hydroxyisobenzofuran-1(3H)-one

[0493] To a mixture of 5-Bromo-4-iodo-3H-isobenzofuran-1-one (**4**, 4 g, 1 eq), sodium hydroxide (2.3 g, 5 eq) in water (40 mL, 1.5 M) and N,N-dimethylacetamide (20 ml) was added cuprous oxide (0.338 g, 0.2 eq). The reaction mixture was heated to 80 °C and held for 12 h. TLC (Hexane : ethyl acetate = 1:1, Rf = 0.3) showed the reaction was completed. The reaction mixture neutralized using 1 (N) hydrochloride solution and extracted with ethyl acetate (40 mL x 2), washed with brine (150 mL), and then dried over sodium sulfate. The crude product was purified by silica gel column chromatography using 0-100% EtOAc/hexane. 5-Bromo-4-hydroxy-3H-isobenzofuran-1-one (**5**, 50% yield) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO) δ 10.90 (s, 1H), 7.72 (d, J= 8.0 Hz, 1H), 7.23 (d, J= 8.0 Hz, 1H), 5.35 (s, 2H).

Step 4: 1-((9H-fluoren-9-yl)methyl) 4-(tert-butyl) (R)-2-(((5-bromo-1-oxo-1,3 dihydroisobenzofuran-4-yl)oxy)methyl)piperazine-1,4-dicarboxylate

[0494] To a solution of 5-Bromo-4-hydroxyisobenzofuran-1(3H)-one (**5**, 700 mg, 3 mmol, 1 eq.) in 12 mL of THF/ DCM, 1-((9H-fluoren-9-yl)methyl) 4-(tert-butyl) (R)-2-(hydroxymethyl)piperazine-1,4-dicarboxylate (2 gm, 4.5 mmol, 1.5 eq.) and PPh_3 (1.17 gm, 4.5 mmol, 1.5 eq.) was added. The reaction mixture was cooled to 0° C and DIAD (0.9 mL, 4.5 mmol, 1.5 eq.) was added dropwise. The resultant mixture was then stirred overnight at room temperature. The solvent was evaporated at reduced pressure; the crude product was purified by silica gel column chromatography using 0-100% EtOAc/hexane. LC/MS (ESI) m/z: 649.15

Step 5: tert-butyl (R)-3-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)piperazine-1-carboxylate

[0495] To a solution of 1-((9H-fluoren-9-yl)methyl) 4-(tert-butyl) (R)-2-(((5-Bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)piperazine-1,4-dicarboxylate (**6**, 1 gm) was added 20% (v/v) piperidine in DMF (5 mL/gm of SM). The resulting mixture was stirred at room temperature overnight. The mixture was diluted with ethyl acetate and washed with water. The combined organic phases were washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo to give an oil. The crude product was purified by silica gel column chromatography using 0-5% DCM in methanol. Yield 70%. LC/MS (ESI) m/z: 426.08 [M+l]+.

Step 6: tert-butyl (R)-1-oxo-1,3,5a,6,8,9-hexahydroisobenzofuro[4,5-b]pyrazino[1,2-d][1,4]oxazine-7(5H)-carboxylate

[0496] A vial was charged with tert-butyl (R)-3-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)piperazine-1-carboxylate (**7**, 170 mg, 0.38 mmol, 1 eq.), $Pd_2(dba)_3$ (0.1 eq.), XantPhos (0.2 eq.), Cs_2CO_3 (3 eq.) and dioxane (5 mL). The mixture was purged with nitrogen and heated to 100 °C for 6 h. TLC (ethyl acetate: petroleum ether = 1:2) showed reaction was complete. The mixture was diluted with ethyl acetate and washed with water. The organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by silica gel column chromatography using 0-50% EtOAc/hexane. LC/MS (ESI) m/z: 347.15 [M+l]+. Yield 60%

Step 7: (R)-3-(tert-butoxycarbonyl)-7-(hydroxymethyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid:

[0497] To a solution of tert-butyl (*R*)-1-oxo-1,3,5a,6,8,9-hexahydroisobenzofuro[4,5-b]pyrazino[1,2-d][1,4]oxazine-7(5H)-carboxylate (**8**, 346 mg, 1 mmol, 1 eq) in tetrahydrofuran (4 mL) and water (4 mL) was added sodium hydroxide (200 mg, 5 eq). The mixture was stirred at 20 °C for 16 h. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The mixture was adjusted to pH = 5 with aq. hydrochloric acid (1 M) and extracted with ethyl acetate (10 mL x 3). The organic layer was washed with brine (10 x 2 mL) and dried over sodium sulfate. The crude material was not further purified and used as crude for the next steps. LC/MS (ESI) m/z: 365.16

Step 8: tert-butyl (5aR)-3-hydroxy-1-oxo-1,3,5a,6,8,9-hexahydroisobenzofuro[4,5-b]pyrazino[1,2-d][1,4]oxazine-7(5H)-carboxylate

[0498] To a solution of (R)-3-(tert-butoxycarbonyl)-7-(hydroxymethyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid (**9**, 1 eq.) in dichloromethane (10 mL) was added manganese dioxide (15 eq.). The mixture was stirred at 20 °C for overnight. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The mixture was diluted with dichloromethane (10 mL) and filtered through a pad of Celite. The filtrate was concentrated in vacuum. The crude product was purified by silica gel column chromatography. LC/MS (ESI) m/z: 363.16. ^{1}H NMR (400 MHz, CD_3OD) δ 7.32 (d, J = 8.3 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.64 – 6.40 (m, 1H), 4.42 (dd, J = 11.0, 3.0 Hz, 1H), 4.23 – 4.01 (m, 3H), 3.95 (d, J = 12.4 Hz, 1H), 3.34 – 3.23 (m, 1H), 3.08 (brs, 1H), 2.87 (td, J = 12.2, 3.5 Hz, 1H), 2.74 (s, 1H) 1.50 (S, 9H).

Step 9: (R)-3-(tert-butoxycarbonyl)-7-((((S)-2,6-dioxopiperidin-3-yl)amino)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid

[0499] To a mixture of (S) 3-aminopiperidine-2,6-dione (**10**, 1.5 eq., HCl salt) in methanol (2 ml) and dichloromethane (4 ml) was added sodium acetate (4 eq.). The mixture was stirred at 20 °C for 15 min, then tert-butyl (5aR)-3-hydroxy-1-oxo-1,3,5a,6,8,9-hexahydroisobenzofuro[4,5-b]pyrazino[1,2-d][1,4]oxazine-7(5H)-carboxylate (1 eq.) was added and the mixture was stirred for 30 mins. Sodium cyanoborohydride (2 eq.) was added and the mixture was further stirred for 1 hour. LCMS showed the reaction was complete. The mixture was adjusted to pH = 4-5 with an aqueous hydrochloric acid solution (1 M) and extracted with ethyl acetate (10 mL x 3). The crude material was not further purified and used as crude for the next steps. LC/MS (ESI) m/z: 475.21

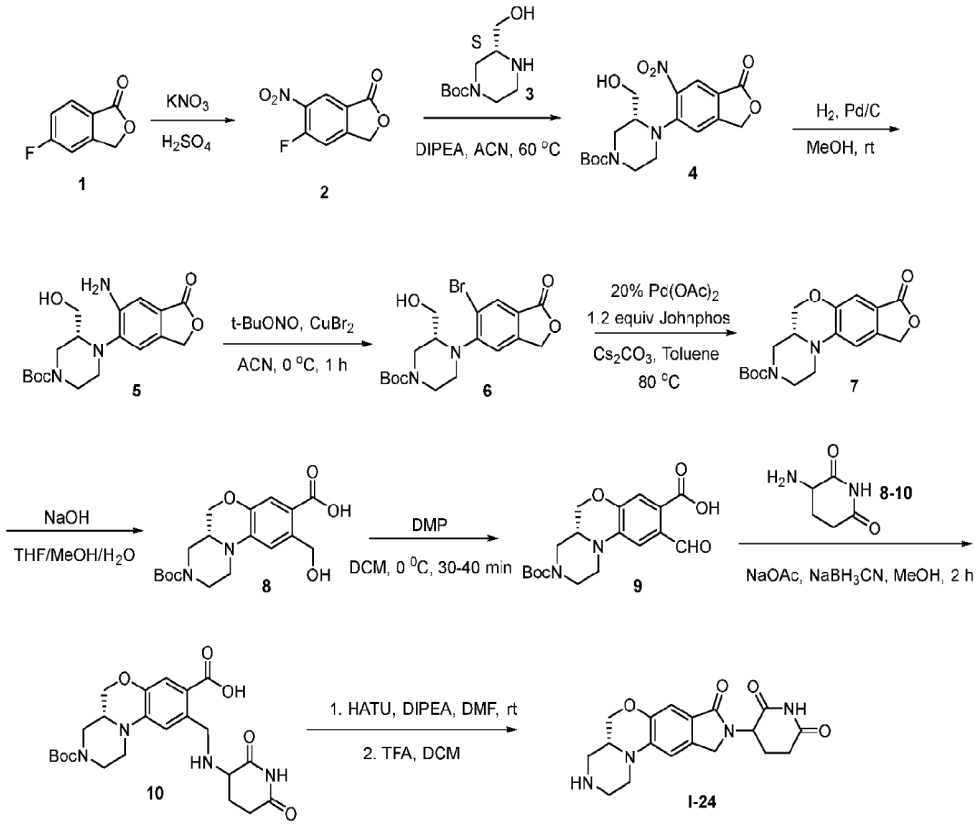
Step 10: tert-butyl (R)-2-((S)-2,6-dioxopiperidin-3-yl)-1-oxo-2,3,5a,6,8,9-hexahydro-1H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindole-7(5H)-carboxylate

[0500] To a solution of (R)-3-(tert-butoxycarbonyl)-7-((((S)-2,6-dioxopiperidin-3-yl)amino)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid (**11**, 90 mg, 0.18 mmol, 1 eq.) in dimethylformamide (5 mL) was added HATU (72 mg, 1.0 eq.) followed by addition of DIPEA (3 eq.). The solution was stirred for 15 mins, at 0 °C. The residue was purified by reverse phase HPLC to get the desired compound **12**. LC/MS (ESI) m/z: 457.20. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.32 (d, J = 8.3 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 5.10 (dd, J = 13.3, 5.2 Hz, 1H), 4.46 – 4.30 (m, 3H), 4.23 – 3.98 (m, 3H), 3.93 (d, J = 12.4 Hz, 1H), 3.22 (ddd, J = 11.2, 8.2, 3.0 Hz, 1H), 3.07 (s, 1H), 2.99 – 2.61 (m, 4H), 2.59 – 2.42 (m, 1H), 2.21 – 2.07 (m, 1H), 1.51 (s, 9H).

Step 11: (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride

[0501] A mixture of *tert-butyl (R)-2-((S)-2,6-dioxopiperidin-3-yl)-1-oxo-2,3,5a,6,8,9-hexahydro-1H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindole-7(5H)-carboxylate* (456 mg, 1.0 mmol, 1 eq.) in HCl/dioxane (10 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated to afford *(S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride* (**I-23**, 400 mg, crude) as white solid.

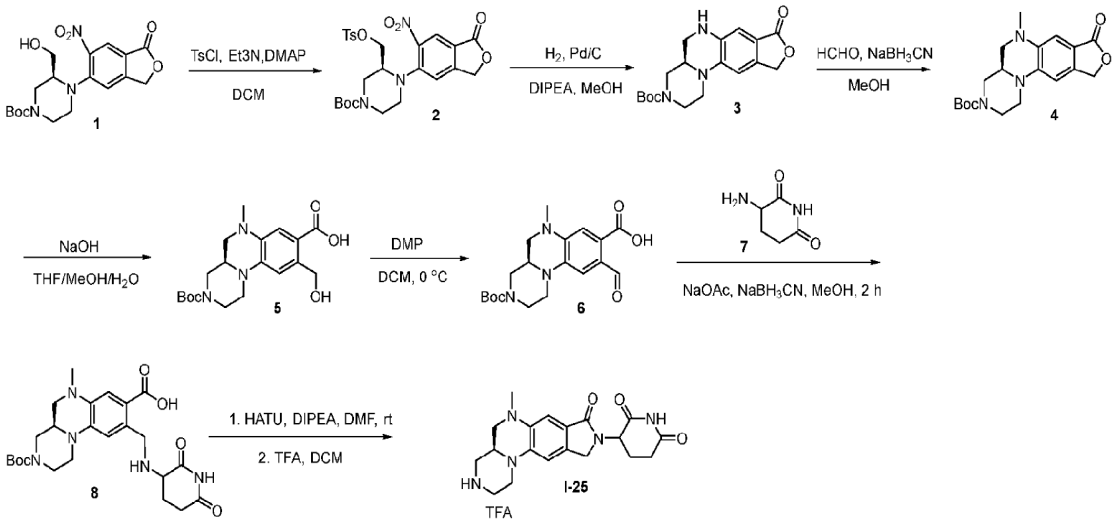
Intermediate 24: 3-((R)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione trifluoroacetat salt



[0502] Intermediate **I-24** was made using the similar procedure for making intermediate **I-10**. LC-MS: $[M+H]^+ = 356.91$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.17 (s, 1H), 7.13 (d, J = 1.7 Hz, 1H), 5.14 – 5.03 (m, 1H), 4.44 – 4.28 (m, 3H), 4.27 – 4.17 (m, 1H), 4.12 – 4.03 (m, 1H), 3.61 – 3.42 (m, 3H), 3.30 – 3.21 (m, 1H), 3.21 – 3.11 (m, 1H), 3.04 – 2.95 (m, 1H), 2.95 – 2.83 (m, 1H), 2.81

– 2.72 (m, 1H), 2.52 – 2.38 (m, 1H), 2.19 – 2.10 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 174.66, 172.46, 172.44, 171.64, 171.61, 146.51, 146.47, 139.24, 139.20, 138.14, 123.98, 123.91, 111.93, 108.73, 108.70, 66.97, 53.71, 53.60, 50.88, 50.86, 44.38, 44.24, 44.20, 43.62, 32.38, 24.13.

Intermediate 25: 3-((S)-6-methyl-8-oxo-2,3,4,4a,5,6,8,10-octahydropyrazino[1,2-a]pyrrolo[3,4-g]quinoxalin-9(1H)-yl)piperidine-2,6-dione trifluoroacetat salt



Step 1: tert-butyl (S)-4-(6-nitro-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-((tosyloxy)methyl)piperazine-1-carboxylate

[0503] To a solution of **1** (1 equiv, 1.49 g) in DCM (30 mL) was TsCl (2.0 equiv, 1.44 g), Et_3N (4.0 equiv, 2.11 mL) and DMAP (0.2 equiv, 92 mg), and the mixture was stirred at rt overnight. TLC (*n*-Hexane:EA = 1:1) indicated the starting material **1**was completely conversion and an new spot detected. Then the reaction mixture was diluted with DCM, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a residue which was purified by silica gel flash chromatography (*n*-Hexane:EA = 100:0 to 60:40). The desired product **2** was obtained as a yellow foam (1.67 g, yield = 81%).

Step 2: tert-butyl (R)-8-oxo-1,2,4,4a,5,6,8,10-octahydro-3H-furo[3,4-g]pyrazino[1,2-a]quinoxaline-3-carboxylate

[0504] To a solution of **2** (1.0 equiv, 1.67 g) in MeOH (20 mL) was added DIPEA (2.0 equiv, 1.06 mL), followed by Pd/C (0.5 equiv, 835 mg). The reaction mixture was degassed and purged with H_2 three times and keep stirred at rt overnight. UPLC-MS showed the starting material completely conversed to desired product **3**. Then the reaction mixture was filtered through Celite, and the

filtrate was concentrated under reduced pressure to give a residue which was purified by silica gel flash chromatography (DCM:MeOH = 100:0 to 95:5). The desired product **3** was obtained as a yellow solid (957 mg, yield = 91%).

Step 3: tert-butyl (R)-6-methyl-8-oxo-1,2,4,4a,5,6,8,10-octahydro-3H-furo[3,4-g]pyrazino[1,2-a]quinoxaline-3-carboxylate

[0505] To a solution of **3** (1.0 equiv, 410 mg) in MeOH/AcOH/DCM (10 mL/1 mL/3 mL) was added HCHO (5.0 equiv, 470 mg), and the mixture was kept stirring for 2 h. Then $NaBH_3CN$ (5.0 equiv, 361 mg) was added. 15 min Later, UPLC-MS showed the starting material **3** all converted to desired product **4**. The reaction mixture was concentrated under reduced pressure, diluted with DCM, washed with brine, dried over Na_2SO_4 and concentrated to give a yellow powder which is directly used in the next step.

Step 4: (R)-3-(tert-butoxycarbonyl)-9-(hydroxymethyl)-6-methyl-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a]quinoxaline-8-carboxylic acid

[0506] **4** (1.0 equiv, 427 mg) was dissolved in THF/MeOH/H_2O (3 mL/3 mL/1 mL), and NaOH (5.0 equiv, 238 mg) was added. The reaction was kept stirring at 40 °C overnight. Then the reaction mixture was concentrated under reduced pressure to remove the solvent. The residue was diluted with 3-4 mL H_2O, followed by acidified with 2 N aq. HCl to PH 3-4. White solid was precipitated, which was collected and dried to give desired product **5** as a white powder 358 mg (yield = 80% in two steps).

Step 5: (R)-3-(tert-butoxycarbonyl)-9-formyl-6-methyl-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a]quinoxaline-8-carboxylic acid

[0507] To a solution of **5** (1.0 equiv, 305 mg) in DCM (20 mL) was added DMP (1.65 equiv, 565 mg) into 3 potions at 0 °C. 30 min Later, UPLC-MS indicated that **5** was completely conversion and a new main peak with desired MS formed, then the reaction was immediately diluted with DCM, washed with brine, dried over and concentrated under reduced pressure to give a crude product **6** which is directly used in the next step.

Step 6: (4aR)-3-(tert-butoxycarbonyl)-9-(((2,6-dioxopiperidin-3-yl)amino)methyl)-6-methyl-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a]quinoxaline-8-carboxylic acid

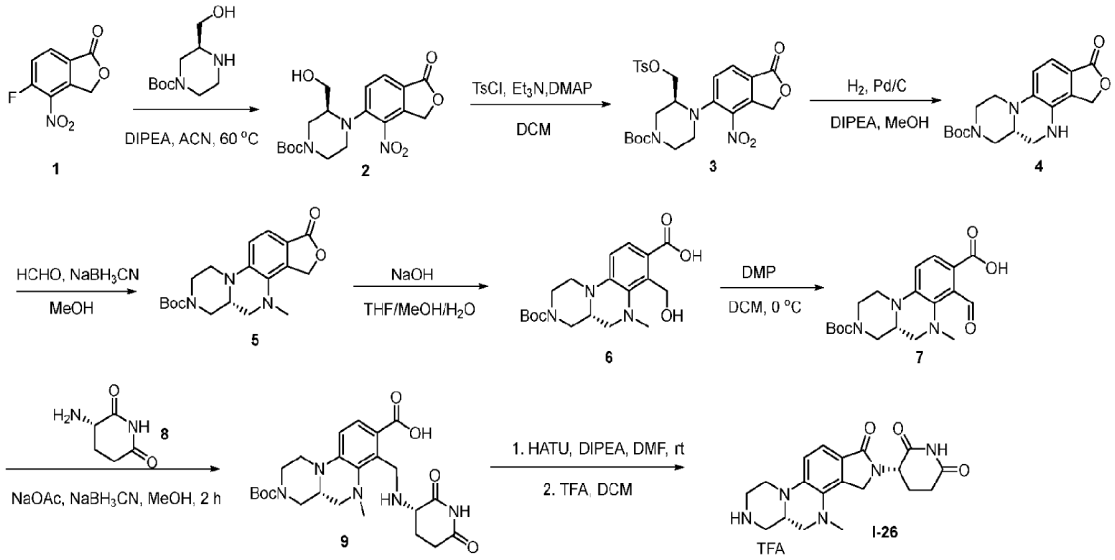
[0508] A mixture of **6** (1.0 equiv, 303 mg), **7** (1.5 equiv, 199.5 mg) and NaOAc (1.5 equiv, 99.4 mg) was dissolved in MeOH (20 mL), and kept stirring at rt for 20 min. Then $NaBH_3CN$ (3.0 equiv, 151 mg) was added in 3 potions. 2 h Later, UPLC-MS showed the starting material **6** was

completely conversion and a new main peak with desired MS formed. Next, the reaction mixture was quenched with 4 mL water and concentrated under reduced pressure to give a residue which was purified by pre-HPLC (20% to 100% acetonitrile (0.1% HCOOH, not TFA) in 80 min, 60 mL/min, 27% acetonitrile come out). The desired product **8** was obtained as a dark solid 138 mg (yield = 35% in two steps) after lyophilization.

Step 7: 3-((S)-6-methyl-8-oxo-2,3,4,4a,5,6,8,10-octahydropyrazino[1,2-a]pyrrolo[3,4-g]quinoxalin-9(1H)-yl)piperidine-2,6-dione trifluoroacetate salt

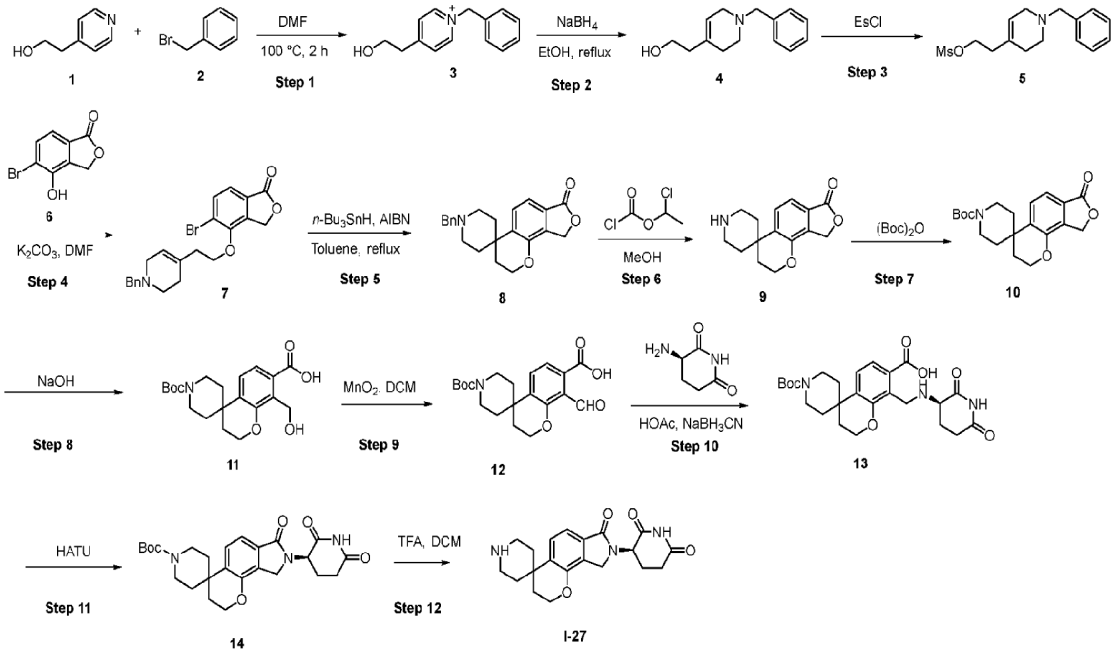
[0509] To a solution of **8** (1.0 equiv, 138 mg) in DMF (5 mL) was added HATU (1.1 equiv, 118 mg) and DIPEA (3.0 equiv, 148 uL), and the reaction was stirred at rt for 20-30 min. UPLC-MS indicated a new main peak with desired MS formed, then quenched with 3 mL water and purified by HPLC-MS (acetonitrile 35% to 100% in 65 min, 60 mL/min, 44% acetonitrile come out). Collected the solution and concentrated to give a solid which was dissolved into TFA/DCM to deprotect the Boc group. The title compound **I-25** was obtained as a light purple solid 40 mg (yield is much higher than here because much product was lost when purified) after removed the solvent and lyophilized. LC-MS: $[M+H]^+$ = 370.02. ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.99 – 6.93 (m, 2H), 5.12 – 5.04 (m, 1H), 4.34 – 4.29 (m, 1H), 4.27 – 4.18 (m, 1H), 3.69 – 3.60 (m, 1H), 3.51 – 3.40 (m, 2H), 3.39 – 3.33 (m, 1H), 3.27 – 3.12 (m, 4H), 3.07 – 3.00 (m, 1H), 2.92 (s, 3H), 2.88 – 2.85 (m, 1H), 2.80 – 2.73 (m, 1H), 2.51 – 2.38 (m, 1H), 2.18 – 2.10 (m, 1H).

Intermediate 26: (3S)-3-(4-methyl-1-oxo-3,4,5,5a,6,7,8,9-octahydropyrazino[1,2-a]pyrrolo[3,4-f]quinoxalin-2(1H)-yl)piperidine-2,6-dione trifluoroacetate salt



[0510] Intermediate **I-26** was made using the similar procedure for making intermediate **I-25**. LC-MS: $[M+H]^+$ = 370.28. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.32 (dd, J = 8.4, 2.3 Hz, 1H), 7.09 (dd, J = 8.6, 2.5 Hz, 1H), 5.14 – 5.04 (m, 1H), 4.63 – 4.44 (m, 2H), 4.30 – 4.16 (m, 1H), 3.60 – 3.51 (m, 1H), 3.49 – 3.39 (m, 2H), 3.29 – 3.21 (m, 2H), 3.16 – 3.02 (m, 2H), 2.98 – 2.83 (m, 5H), 2.82 – 2.72 (m, 1H), 2.58 – 2.45 (m, 1H), 2.21 – 2.10 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 174.70, 172.53, 172.50, 171.69, 171.63, 141.77, 141.73, 133.94, 133.82, 133.63, 124.97, 118.36, 118.32, 115.17, 53.85, 53.82, 53.67, 53.63, 47.98, 47.86, 46.28, 44.83, 44.39, 43.81, 43.75, 32.37, 24.03, 23.99.

Intermediate 27: 3-(7'-oxo-2',3',7',9'-tetrahydro-8'H-spiro[piperidine-4,4'-pyrano[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione trifuluoroacetate salt



Step 1-2:

[0511] To a solution of 2-(pyridin-4-yl)ethan-1-ol (**1**, 10 g, 91.6 mmol, 1.0 eq.) in DMF (40 mL) was added BnBr (15.3 g, 108 mmol, 1.1 eq.). The mixture was allowed to heat to 100°C and stirred 3 h. TLC showed no starting material remained and a new spot formed. The residue was dissolved in EtOH (150 mL), then 4.0 g of sodium borohydride (119.1 mmol, 1.3 eq.) was added portionwise at 0°C. The mixture was continued to stir at 0°C for 1 h and then at reflux for 2 h. The solvent was evaporated under reduced pressure, then water was added, and the mixture was extracted with EA. The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatograph (DCM:MeOH = 100:0-30:1) to afford 10 g of product **4** (Viscous oil, 2 steps, yield 56%). LC-MS: 218 $[M+H]^+$.

Step 3:

[0512] To a solution of compound **4** (10 g, 1 eq.) in DCM (200.0 mL) was added DMAP (0.1 eq.) and TEA (2 eq.) at 0 °C. Then EsCl (1.5 eq.) was slowly added into and the mixture was stirred at R.T. for 1 h. The reaction was partitioned between EtOAc and water. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatograph to give compound **5** as a yellow solid (10 g, yield 70%). LC-MS: 310 $[M+H]^+$.

Step 4:

[0513] To a solution of compound **6** (10 g, 1.0 eq.) in 100 mL of DMF, compound **5** (16.2 g, 1.2 eq.) and K_2CO_3 (1.6 eq.) was added. The reaction mixture was heated to 70°C and stirred overnight. The reaction mixture was poured into ice-water and extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate. The solvent was evaporated at reduced pressure and the crude product was purified by silica gel column chromatography using 0-100% EtOAc/hexane. The desired product **7** was obtained as a yellow foam (11 g, yield 60%). 428/430 $[M+H]^+$.

Step 5:

[0514] To a solution of **7** (5 g, 1.0 eq.) in toluene (50 mL) was added n-Bu_3SnH (13.6 g, 4.0 eq.) and AIBN (0.4 g, 0.1 eq.). The mixture was heated to reflux and stirred overnight. TLC (PE:EA = 1:1) showed no starting material remained and new spots formed. The reaction mixture was poured into saturated aq. KF solution (100 mL) and stirred overnight. Then, the reaction mixture was extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate. The crude product was purified by silica gel column chromatography (DCM:MeOH = 50:1) to give compound **8** was obtained as a white solid (2 g, 50% yield). LC-MS: 350 $[M+H]^+$.

Step 6-7:

[0515] To a solution of **8** (3.0 g, 1.0 eq.) in DCE (100 mL) was added α-chloroethyl chloroformate (ACE-Cl, 1.2 eq.) at 0 °C and then refluxing the mixture for 15 h. The intermediate ACE-piperidine formed and is usually de*ACE*ylated directly to **9** by evaporating the reaction mixture in vacuo and then heating the residue in MeOH. The residue was dissolved in THF (100 mL), then trimethylamine (3.0 eq.) and Boc_2O (1.3 eq.) was added. The mixture was continued to stir for 3 h at room temperature. The solvent was evaporated under reduced pressure, then water was added, and the mixture was extracted with EA. The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatograph to afford **10** (1.5 g, 2 steps, yield 50%). LC-MS: 360 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform-d) δ 7.47 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 5.24 (s, 2H), 4.16 (t, J = 6.7 Hz, 2H), 3.88 (m, 2H), 3.51 (m, 2H), 2.52 (t, J = 6.8 Hz, 2H), 2.13 (m, 2H), 1.61 (m, 2H), 1.46 (s, 9H).

Step 8:

[0516] To a solution of compound **10** (2 g, 1 eq.) in tetrahydrofuran (10 mL) and water (10 mL) was added sodium hydroxide (1.2 g, 5 eq.). The mixture was stirred at 20 °C for 16 h. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The mixture was adjusted to pH = 5-6 with

aq. hydrochloric acid (1 M) and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The crude product **11** was not further purified and used as crude for the next step.

Step 9:

[0517] To a solution of compound **11** (2 g, crude, 1 eq.) in dichloromethane (30 mL) was added manganese dioxide (20 eq.). The mixture was stirred at 20 °C for about 1 h. TLC showed reaction was complete. The mixture was diluted with dichloromethane and filtered through a pad of Celite. The filtrate was concentrated in vacuum. The crude product was purified by silica gel column chromatography (DCM: MeOH = 10:1). The desired compound **12** was obtained as yellow solid. (1.2 g, 2 steps, 60%). LC-MS: 376 $[M+H]^+$.

Step 10:

[0518] To a mixture of compound **12** (532 mg, 1.0 eq.) in methanol (5 mL) and dichloromethane (5 mL) was added 3-aminopiperidine-2,6-dione (698 mg, 3 eq., HCl salt), AcONa (698 mg, 6.0 eq.) and AcOH (0.85 mL, 10.0 eq.). The mixture was stirred at 25 °C for 1 h, then sodium cyanoborohydride (268 mg, 3.0 eq.) was added and the mixture was further stirred for 30 min. LCMS showed the reaction was complete. Next, the reaction mixture was quenched with water and concentrated under reduced pressure to give a residue which was purified by pre-HPLC (20% ~ 50% ACN, neutral). The desired product **13** as a solid (415 mg, yield = 60%) after lyophilization. LC-MS: 488 $[M+H]^+$.

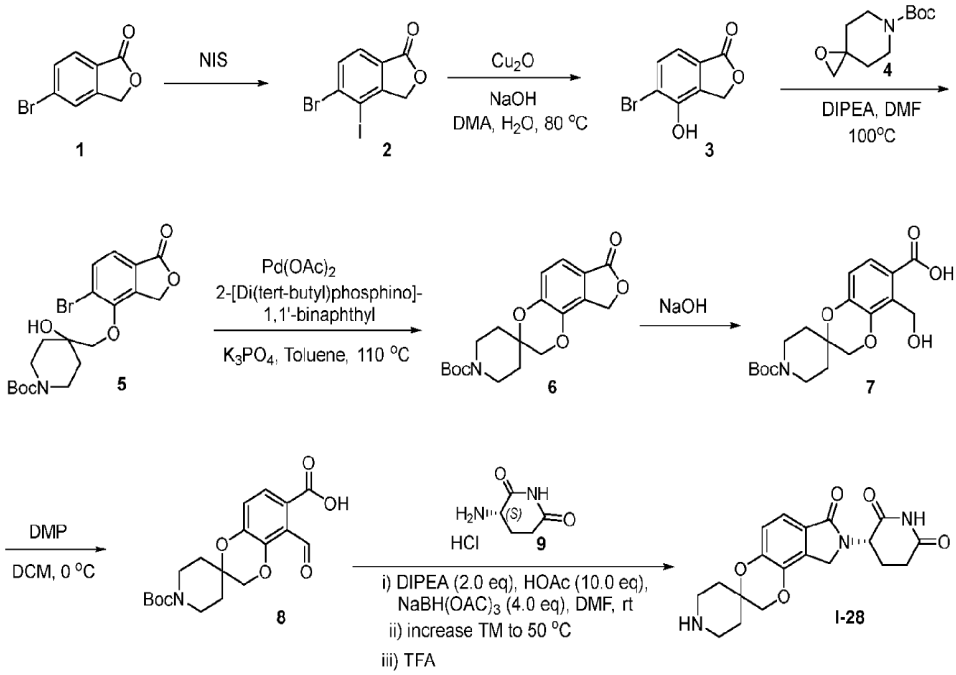
Step 11:

[0519] To a solution of compound **13** (300 mg 1.0 equiv) in DMF (5 mL) was added HATU (300 mg, 1.3 equiv) and DIPEA (0.35 mL, 3.0 equiv), and the reaction was stirred at rt for 30 min. UPLC-MS indicated a new main peak with desired MS formed, then quenched with water and the mixture was extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate. Compound **14** was obtained as a brown solid (230 mg, 75% yield). LC-MS: 470 $[M+H]^+$.

Step 12:

[0520] Compound **14** was treated with TFA in DCM at room temperature to de-protect the N-Boc group to provide the cereblon ligand **I-27**. LC/MS (ESI) m/z: 370.17. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.45 (d, J = 1.2 Hz, 2H), 5.22 (dd, J = 13.2, 5.1 Hz, 1H), 4.40 (d, J = 16.4 Hz, 1H), 4.31 – 4.20 (m, 3H), 4.11 (brs, 1H), 3.06 – 2.78 (m, 4H), 2.37 (qd, J = 13.1, 5.0 Hz, 1H), 2.22 (dtd, J = 13.1, 5.3, 2.7 Hz, 1H), 2.17 – 2.04 (m, 3H), 1.60-1.50 (s, 4H).

Intermediate 28: (S)-3-(7'-oxo-7',9'-dihydro-2'H,8'H-spiro[piperidine-4,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione



Step1: 5-bromo-4-iodoisobenzofuran-1(3H)-one

[0521] To a solution of **1** (10 g, 1.0 equiv) in CF_3SO_3H (50 mL) was added NIS (1.5 equiv) potionwise at 0 °C. The reaction was stirred at rt overnight. Then the reaction mixture was poured into ice-water, and gray solid was precipitated, which is collected by filtration and washed with water. The filter cake was dissolved in DCM, washed with aquous $Na_2S_2O_3$, brine, dried over Na_2SO_4 and concentrated to afford a crude product. Further purification by silica gel column chromatography to give the desired product as a white solid 6.55 g.

Step 2: 5-bromo-4-hydroxyisobenzofuran-1(3H)-one

[0522] A mixture of **2** (6.55 g, 1.0 equiv), Cu_2O (553 mg, 0.2 equiv) and NaOH (3.86 g, 5.0 equiv) in DMA/H_2O (40 mL/20 mL) was degassed with N_2 and stirred at 80 °C under N_2 atmosphere overnight. Then the reaction mixture was cooled to rt, neutralized with 2N aq. HCl, extracted with EA, washed with brine, dried over Na_2SO_4, and concentrated to give the crude product, which is purified by silica gel column chromatography to provide compound **3** as a yellow solid 3.67 g (yield = 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 5.34 (s, 2H).

Step3: tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)-4-hydroxypiperidine-1-carboxylate

[0523] To a solution of **3** (500 mg, 1.0 equiv) and **4** (931 mg, 2.0 equiv) in DMF (15 mL) was added DIPEA (3.8 mL, 10.0 equiv), which was stirred at 100 °C for 2 days. Then the reaction mixture was cooled to rt, diluted with EA, washed with brine, dried over Na_2SO_4 and concenterated. The crude product was purified by silica gel column chromatography to give compound **5** as a brown oil 1.03 g, yield > 95%. LC-MS: 344.01 $[M+H]^+$.

Step 4: tert-butyl 7'-oxo-7',9'-dihydro-2'H-spiro[piperidine-4,3'-[1,4]dioxino[2,3-e]isobenzofuran]-1-carboxylate

[0524] A mixture of **5** (870 mg, 1.0 equiv), $Pd(OAc)_2$ (51 mg, 0.2 equiv), 2-[Di(tert-butyl)phosphino]-1,1'-binaphthyl (135 mg, 0.3 equiv) and K_3PO_4 (719 mg, 3.0 equiv) in Toluene (12 mL) was degassed with N_2 and then was stirred at 110 °C under N_2 atmosphere overnight. The reaction mixture was filtered through celite, and the filtration was concentrated under reduced pressure. The result mixture was purified by silica gel column chromatography to give compound **6** as a white solid 540 mg, yield = 73%. LC-MS: 362.21 $[M+H]^+$.

Step 5: 1'-(tert-butoxycarbonyl)-5-(hydroxymethyl)-3H-spiro[benzo[b][1,4]dioxine-2,4'-piperidine]-6-carboxylic acid

[0525] To a solution of **6** (298 mg, 1.0 equiv) in THF/MeOH/H_2O (5 mL/5 mL/3 mL) was added NaOH (330 mg, 10 equiv). The reaction was stirred at rt for 8 h, then concentrated to remove most of the THF/MeOH. The residue was diluted with 4 mL water, followed by neutralization with 2 N aq HCl to PH 4-6, then extracted with DCM. Then combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated to give the desired product **7** as a white solid 284 mg, which was directly used in the next step.

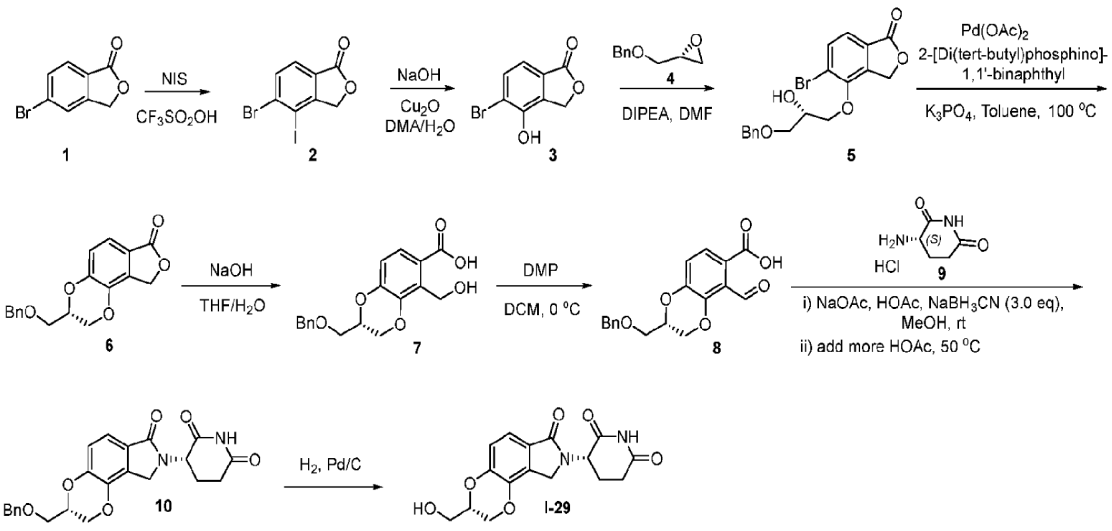
Step 6: 1'-(tert-butoxycarbonyl)-5-formyl-3H-spiro[benzo[b][1,4]dioxine-2,4'-piperidine]-6-carboxylic acid

[0526] To a solution of **7** (284 mg, 1.0 equiv) in DCM (15 mL) was added DMP (475 mg, 1.5 equiv) potionwise at 0 °C. 5 h Later, the reaction mixture was washed with brine, dried over Na_2SO_4, and concentrated to give the crude product **8**, which was directly used in the next step.

*Step 7: (S)-3-(7'-oxo-7',9'-dihydro-2'H,8'H-spiro[piperidine-4,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione (**I-28**)*

[0527] To a suspension of **9** (46 mg, 2.0 equiv) in DMF (4 mL) was added DIPEA (49 uL, 2.0 equiv), which was stirred at rt for 10 min, followed by addition of AcOH (423 uL, 10.0 equiv). 10 min Later, crude compound **8** (53 mg, 1.0 equiv) was added, and the resulted mixture was stirred at rt for 15 min. Subsequently, $NaBH(OAc)_3$ (119 mg, 4.0 equiv) was added, and the reaction mixture was stirred overnight. Then the reaction mixture was heated to 50 °C and kept stirring for 12 h. Next, the reaction mixture was concentrated to remove AcOH, and purified by pre-HPLC to give a light purple solid 33 mg. LC-MS: 472.17 $[M+H]^+$. Finally, intermediate **I-28** was obtained after treatment with TFA. LC-MS: 372.17 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.37 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.51 – 4.35 (m, 2H), 4.17 (d, J = 2.0 Hz, 2H), 3.42 – 3.35 (m, 4H), 2.96 – 2.84 (m, 1H), 2.82 – 2.72 (m, 1H), 2.56 – 2.42 (m, 1H), 2.21 – 2.06 (m, 3H), 2.01 – 1.88 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 174.64, 172.26, 171.11, 145.75, 138.95, 131.85, 126.85, 119.67, 118.32, 71.56, 53.74, 46.27, 40.52, 40.49, 32.37, 28.91, 28.85, 24.05.

Intermediate 29: (S)-3-((S)-3-(hydroxymethyl)-7-oxo-2,3,7,9-tetrahydro-8H-[1,4]dioxino[2,3-e]isoindol-8-yl)piperidine-2,6-dione



Step1: 5-bromo-4-iodoisobenzofuran-1(3H)-one

[0528] To a solution of **1** (10 g, 1.0 equiv) in CF_3SO_3H (50 mL) was added NIS (1.5 equiv) potionwise at 0 °C. The reaction was stirred at rt overnight. Then the reaction mixture was poured into ice-water, and gray solid was precipitated, which is collected by filtration and washed with water. The filter cake was dissolved in DCM, washed with aquous $Na_2S_2O_3$, brine, dried over

Na_2SO_4 and concentrated to afford a crude product. Further purification by silica gel column chromatography to give the desired product as a white solid 6.55 g.

Step 2: 5-bromo-4-hydroxyisobenzofuran-1(3H)-one

[0529] A mixture of **2** (6.55 g, 1.0 equiv), Cu_2O (553 mg, 0.2 equiv) and NaOH (3.86 g, 5.0 equiv) in DMA/H_2O (40 mL/20 mL) was degassed with N_2 and stirred at 80 °C under N_2 atmosphere overnight. Then the reaction mixture was cooled to rt, neutralized with 2N aq. HCl, extracted with EA, washed with brine, dried over Na_2SO_4, and concentrated to give the crude product, which is purified by silica gel column chromatography to provide compound **3** as a yellow solid 3.67 g (yield = 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 5.34 (s, 2H).

Step3: (S)-4-(3-(benzyloxy)-2-hydroxypropoxy)-5-bromoisobenzofuran-1(3H)-one

[0530] To a solution of **3** (500 mg, 1.0 equiv) and **4** (1015 uL, 3.0 equiv) in DMF (10 mL) was added DIPEA (1.9 mL, 5.0 equiv), which was stirred at 100 °C for 2 days. Then the reaction mixture was cooled to rt, diluted with EA, washed with brine, dried over Na_2SO_4 and concenterated. The crude product was purified by silica gel column chromatography to give compound **5** as a light yellow oil 785 mg, yield = 91.5%.

Step 4: tert-butyl 7'-oxo-7',9'-dihydro-2'H-spiro[piperidine-4,3'-[1,4]dioxino[2,3-e]isobenzofuran]-1-carboxylate

[0531] A mixture of **5** (785 mg, 1.0 equiv), $Pd(OAc)_2$ (0.2 equiv, 90 mg), 2-[Di(tert-butyl)phosphino]-1,1'-binaphthyl (0.3 equiv, 238 mg) and K_3PO_4 (1270 mg, 3.0 equiv) in Toluene (12 mL) was degassed with N_2 and then was stirred at 100 °C under N_2 atmosphere overnight. The reaction mixture was filtered through celite, and the filtration was concentrated under reduced pressure. The result mixture was purified by silica gel column chromatography to give compound **6** as a light yellow solid 465 mg, yield = 74%. LC-MS: 313.01 $[M+H]^+$.

Step 5: (S)-2-((benzyloxy)methyl)-5-(hydroxymethyl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid

[0532] To a solution of **6** (465 mg, 1.0 equiv) in THF/MeOH/H_2O (6 mL/6 mL/6 mL) was added NaOH (358 mg, 6.0 equiv). The reaction was stirred at rt overnight, then concentrated to remove most of the THF/MeOH. The residue was diluted with 4 mL water, followed by neutralization with 2 N aq HCl to PH 4-6, then extracted with DCM. Then combined organic layer was washed with

brine, dried with Na_2SO_4, and concentrated to give the desired product **7** as a light yellow foam 376 mg, which was directly used in the next step.

Step 6: (S)-2-((benzyloxy)methyl)-5-formyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid

[0533] To a solution of **7** (376 mg, 1.0 equiv) in DCM (15 mL) was added DMP (870 mg, 1.8 equiv) potionwise at 0 °C. 1 h Later, the reaction mixture was washed with brine, dried over Na_2SO_4, and concentrated to give the crude product **8**, which was directly used in the next step.

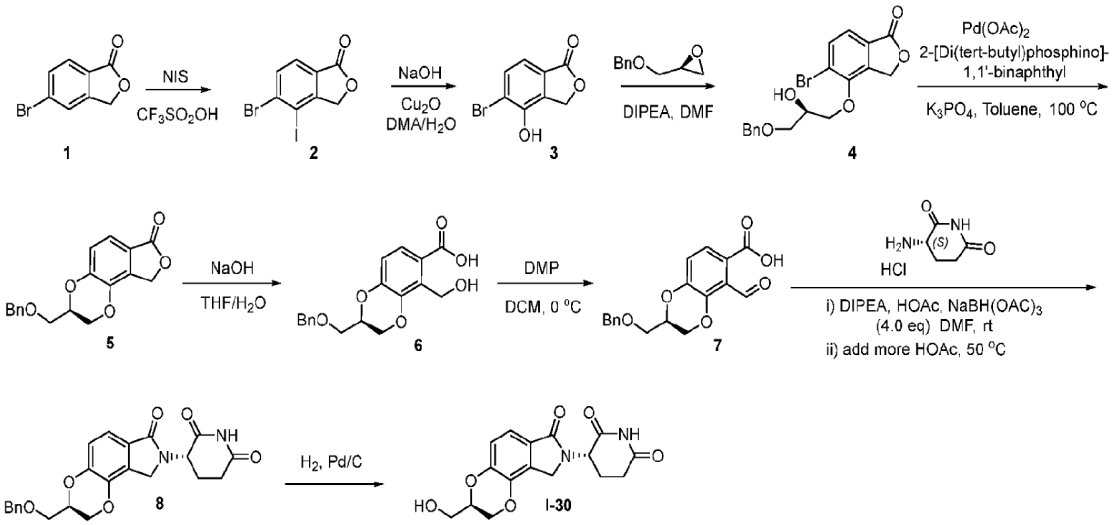
*Step 7: (S)-3-((S)-3-((benzyloxy)methyl)-7-oxo-2,3,7,9-tetrahydro-8H-[1,4]dioxino[2,3-e]isoindol-8-yl)piperidine-2,6-dione (**I-29**)*

[0534] To a solution of **9** (279 mg, 2.0 equiv) and NaOAc (139 mg, 1.5 equiv) in MeOH (8 mL) was added **8** (370 mg, 1.0 equiv) and AcOH (322 uL, 5.0 equiv). 15 min Later, $NaBH_3CN$ (211 mg, 3.0 equiv) was added in potionwise, and the resulted mixture was stirred at rt for 6 h. Then more AcOH (3.22 mL, 50 equiv) was added, and the reaction mixture was stirred at 50 °C for 3 h. Next, the reaction mixture was concentrated to remove AcOH, and purified by pre-HPLC to give product **10** as a light-yellow oil 222 mg (yield = 35%). LC-MS: 423.16 $[M+H]^+$.

Step 8: (S)-3-((S)-3-(hydroxymethyl)-7-oxo-2,3,7,9-tetrahydro-8H-[1,4]dioxino[2,3-e]isoindol-8-yl)piperidine-2,6-dione

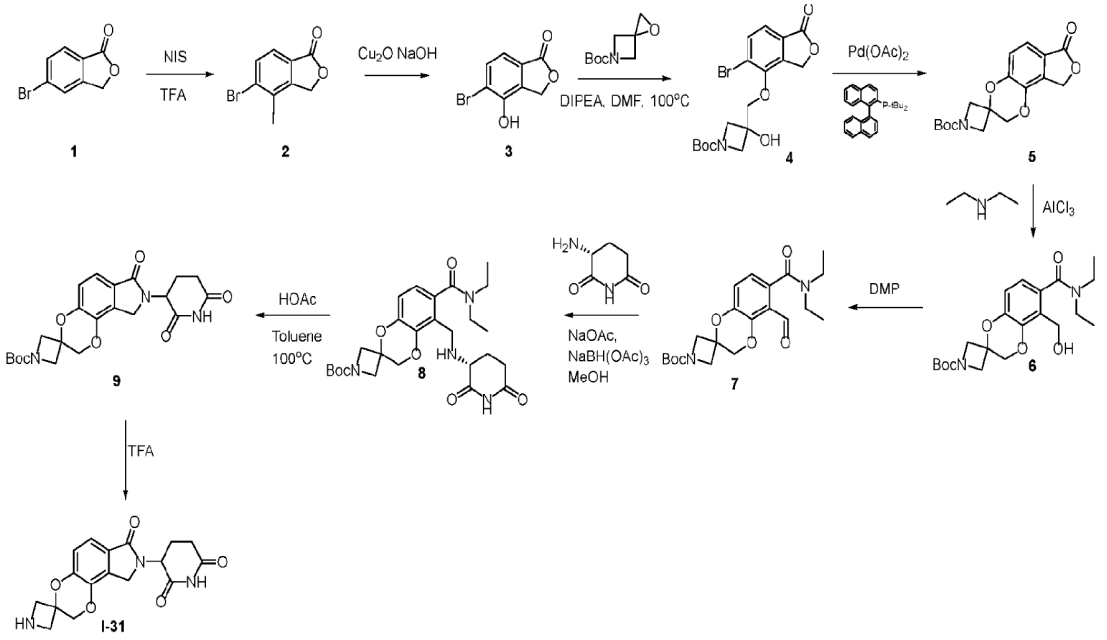
[0535] A suspension of **10** (212 mg, 1.0 equiv), Pd/C (10% Pd in C powder, 212 mg) in MeOH was gassed with H_2 and stirred under H_2 atmosphere for 3 h. The reaction mixture was filtered, and the filtration was concentrated to give intermediate **I-29** as a white solid 127 mg. LC-MS: 333.11 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.31 (d, J = 8.2 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 5.10 (dd, J = 13.3, 5.2 Hz, 1H), 4.47 – 4.36 (m, 3H), 4.32 – 4.24 (m, 1H), 4.21 – 4.12 (m, 1H), 3.83 – 3.78 (m, 2H), 2.95 – 2.82 (m, 1H), 2.81 – 2.72 (m, 1H), 2.56 – 2.41 (m, 1H), 2.20 – 2.10 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 174.69, 172.28, 171.35, 148.12, 139.73, 131.67, 126.17, 119.25, 117.68, 75.72, 66.76, 61.72, 53.70, 46.25, 32.39, 24.08.

Intermediate 30: (S)-3-((R)-3-(hydroxymethyl)-7-oxo-2,3,7,9-tetrahydro-8H-[1,4]dioxino[2,3-e]isoindol-8-yl)piperidine-2,6-dione



[0536] The procedure for making intermediate **I-30** is same as that for making intermediate **I-29**. Intermeidate **I-30** was obtained as a white solid 193 mg. LC-MS: 333.12 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.31 (d, J = 8.2 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 5.10 (dd, J = 13.3, 5.2 Hz, 1H), 4.48 – 4.32 (m, 3H), 4.32 – 4.25 (m, 1H), 4.21 – 4.13 (m, 1H), 3.81 (dd, J = 5.1, 1.5 Hz, 2H), 2.95 – 2.83 (m, 1H), 2.82 – 2.72 (m, 1H), 2.56 – 2.42 (m, 1H), 2.20 – 2.10 (m, 1H).

Intermediate 31: 3-(7'-oxo-7',9'-dihydro-2'H,8'H-spiro[azetidine-3,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione



[0537] *Step 1 and Step 2 are same as* ***Intermediate 28***

Step3: tert-butyl 3-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)-3-hydroxyazetidine-1-carboxylate

[0538] To a solution of **3** (1 equiv) in DMF (c1 = 0.2 mol/L). DIPEA (10 equiv) and epoxide (1.5 equiv) was added into the flask. The reaction was heated to 100°C. The reaction was detected by UPLC-MS. Concentrated directly and purify by silica gel chromatography to give **4** (96% yield).

Step 4: tert-butyl 7'-oxo-7',9'-dihydro-2'H-spiro[azetidine-3,3'-[1,4]dioxino[2,3-e]isobenzofuran]-1-carboxylate

[0539] To a solution of 4 (1 equiv) in toluene (c1 = 0.1 mol/L). Pd(OAc)2 (0.1 equiv), Ligand (0.11 equiv) and K3PO4 (3 equiv) was added into the flask under N2. The reaction was heated to 140°C under N2 for 4h. TLC showed reaction was completed. Quenched with saturated NaHCO3, The organic phase was separated. EA was added to the mixture, the resulting mixture was washed by brine. The conbined organic phase was dried by MgSO4. Filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (90% yield) .

Step 5: *tert-butyl 6'-(diethylcarbamoyl)-5'-(hydroxymethyl)-3'H-spiro[azetidine-3,2'-benzo[b][1,4]dioxine]-1-carboxylate*

[0540] To a suspension of aluminium trichloride (1.3 equiv.) in DCM (c_{AlCl3} = 0.5 mol/L), diethylamine (2.5 equiv.) was added at 0 °C and the mixture was stirred for additional 30 min. A solution of **5** (1.0 eq.) in DCM (c_{10} = 1 mol/L), was added and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into 300 mL saturated aqueous NH_4Cl. The organic layers were combined and washed with 200 mL saturated aqueous NH_4Cl, dried over anhydrous $MgSO_4$, and concentrated in vacuum. The obtained residue was purified by silica gel chromatography to give **6** (85% yield).

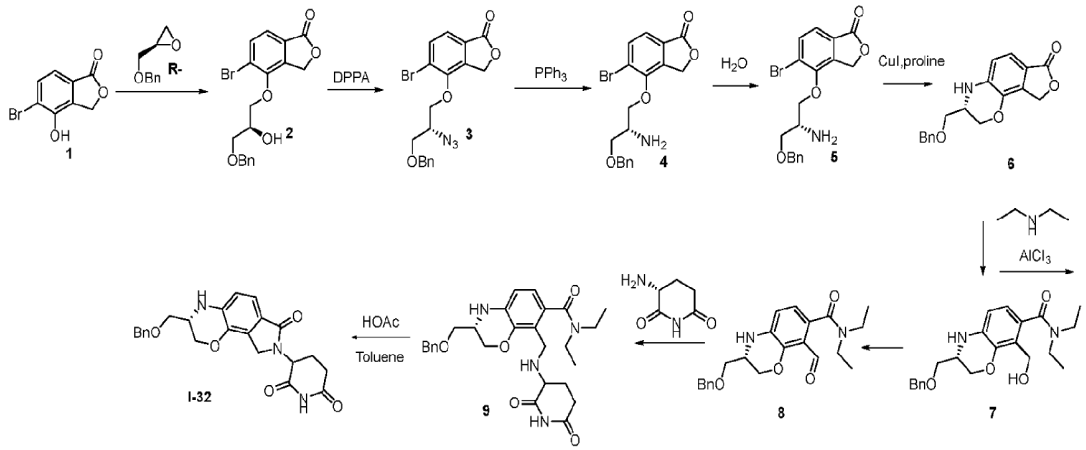
Step 6: *tert-butyl 6'-(diethylcarbamoyl)-5'-formyl-3'H-spiro[azetidine-3,2'-benzo[b][1,4]dioxine]-1-carboxylate*

[0541] To a solution of **6** (1 equiv) in DCM (c_1 = 0.1 mol/L). DMP (1.1 equiv) was added into the flask at room temperature. Reaction was detected by UPLM-MS. Quenched with saturated $NaHCO_3$. EA was added to the mixture, The organic phase was separated. the resulting mixture was washed by brine. The combined organic phase was dried by $MgSO_4$. Filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give **7** (90%).

Step 7 to Step 9: *3-(7'-oxo-7',9'-dihydro-2'H,8'H-spiro[azetidine-3,3'-[1,4]dioxino[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione*

[0542] To a solution of **7** (1 equiv) in MeOH (c_1 = 0.2 mol/L). NaOAc (1.0 equiv) and (S)-3-Amino-piperidine-2,6-dione hydrochloride NaOAc (1.0 equiv), $NaCNBH_3$ (1.0 equiv) was added into the flask at room temperature. Reaction was detected by UPLM-MS (about 3 hours). Remove solvent under vacuum. The residue was dissolved in toluene. HOAc(15 equiv) was added into flask. The rection was heated at 110°C and stirred for 12hour. **9** was purified by HPLC(TFA condition). 1.0 equiv TFA was added and concentrated **9** to get de-Boc **I-31** (70% yield in three steps).

Intermediate 32: (R)-3-(3-((benzyloxy)methyl)-7-oxo-3,4,7,9-tetrahydro-3l3-[1,4]oxazino[6,5-e]isoindol-8(2H)-yl)piperidine-2,6-dione



Step1: (S)-4-(3-(benzyloxy)-2-hydroxypropoxy)-5-bromoisobenzofuran-1(3H)-one

[0543] To a solution of **1** (1 equiv) in DMF (c_1 = 0.2 mol/L). DIPEA (10 equiv) and epoxide (1.5 equiv) was added into the flask. The reaction was heated to 100°C. The reaction was detected by UPLC-MS. Concentrated directly and purify by silica gel chromatography to give **2** (89% yield).

Step 2: (R)-4-(2-azido-3-(benzyloxy)propoxy)-5-bromoisobenzofuran-1(3H)-one

[0544] To a solution of **2** (1 equiv) in THF (c_2 = 0.1 mol/L). PPh_3 (2 equiv) and DPPA (2 equiv) was added into the flask. Then dropped DIAD (2 equiv). The reaction was quenched with saturated $NaHCO_3$. EA was added to the mixture, the organic phase was separated. The resulting mixture was washed by brine. The combined organic phase was dried by $MgSO_4$. Filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give **7** (80%)

Step 3 to 4: (R)-4-(2-amino-3-(benzyloxy)propoxy)-5-bromoisobenzofuran-1(3H)-one

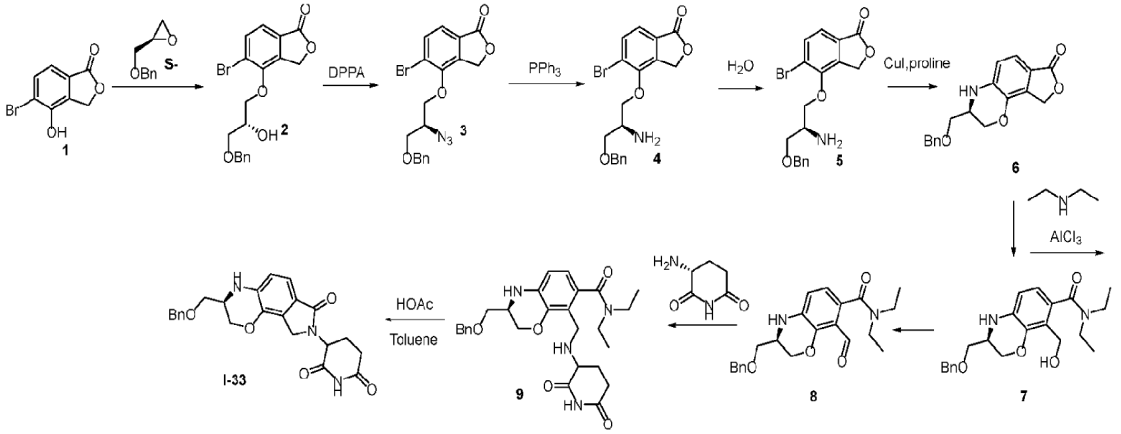
[0545] To a solution of **3** (1 equiv.) in THF (c_3 = 0.2 mol/L). PPh_3 (2 equiv.) was added into the flask. The reaction was heated to 80°C for 8h. Then added H_2O (20 equiv.) and heated for 24h. Concentrated directly and purify by silica gel chromatography to give **4** (78% yield).

Step 5: (S)-3-((benzyloxy)methyl)-3,4-dihydro-2H-isobenzofuro[4,5-b][1,4]oxazin-7(9H)-one

[0546] To a solution of **5** (1 equiv.) in DMF (c_5 = 0.2 mol/L). CuI (0.1 equiv.) and proline (0.1 equiv.) was added into the flask. The reaction was heated under H_2 at 100°C for 3h. The reaction was quenched with saturated $NaHCO_3$. EA was added to the mixture, the organic phase was separated. The resulting mixture was washed by brine. The combined organic phase was dried by $MgSO_4$. Filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give **6** (45%)

[0547] *Step 6 to 10 are same as **I-31.***

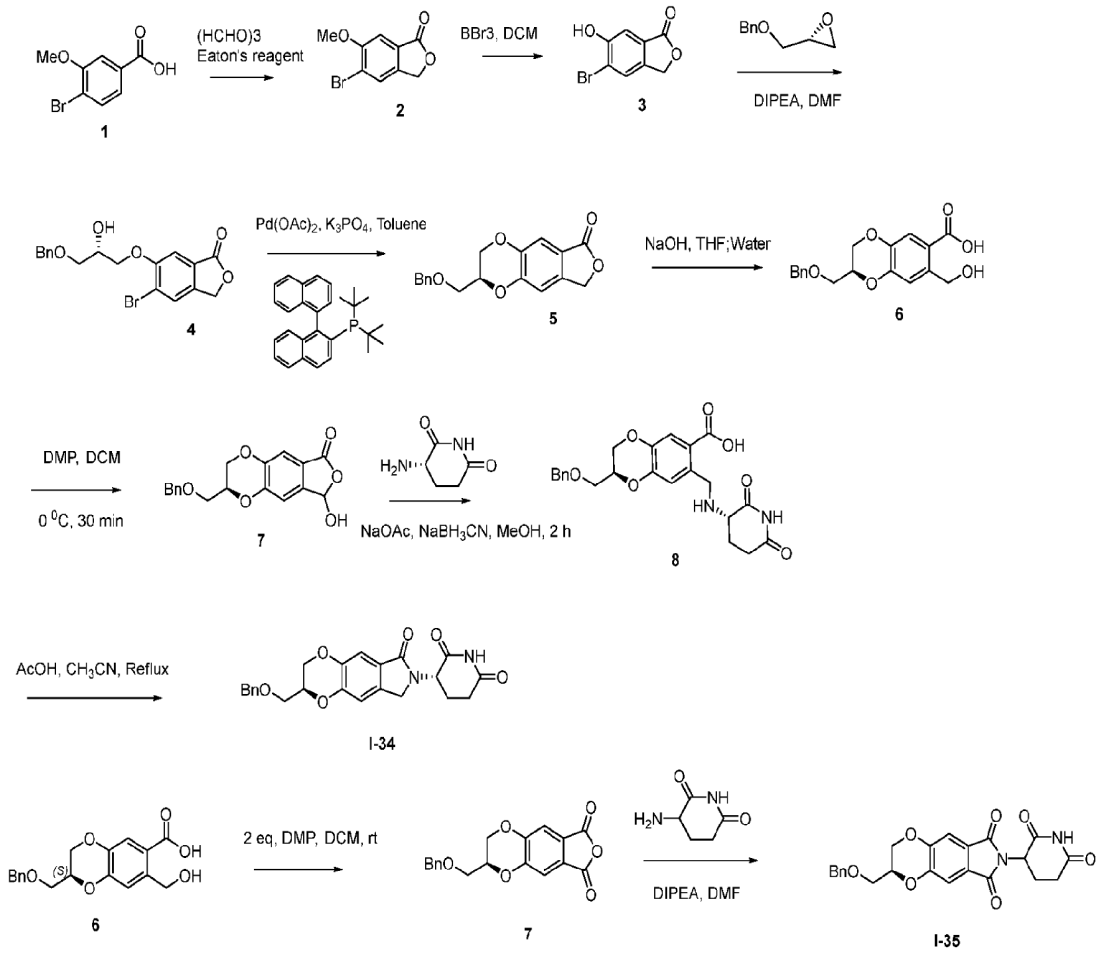
Intermediate 33:



[0548] The procedure for making intermediate **I-33** is same as that for making intermediate **I-32**.

Intermediate 34. (S)-3-((S)-2-((benzyloxy)methyl)-6-oxo-2,3,6,8-tetrahydro-7H-[1,4]dioxino[2,3-f]isoindol-7-yl)piperidine-2,6-dione

Intermediate 35: (2S)-2-((benzyloxy)methyl)-7-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-6H-[1,4]dioxino[2,3-f]isoindole-6,8(7H)-dione



Step 1: 5-bromo-6-methoxyisobenzofuran-1(3H)-one

[0549] To a 100 mL round-bottom flask, Eaton's reagent (30 mL), compound 4-bromo-3-methoxybenzoic acid (**1**, 5 gm, 21.83 mmol) and Paraformaldehyde (1.96 g, 65 mmol) were added in an ice bath. The resulting mixture was stirred and heated to 50 °C for overnight. After being cooled to room temperature, the reaction mixture was poured into ice-cold water (100 mL) and extracted with dichloromethane (3× 60 mL). The combined organic layer was washed with water, saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo, followed purification by silica gel chromatography to give compound **2** in 70% yield.

Step 2: 5-bromo-6-hydroxyisobenzofuran-1(3H)-one

[0550] Over a solution of 5-bromo-6-methoxyisobenzofuran-1(3H)-one (2 g, 8.29 mmol) in dry CH_2Cl_2 (36 mL) under N_2 atmosphere at -20 °C was added boron tribromide (16.6 mL 1M DCM, 16.6 mmol). Then the solution was stirred at rt for overnight. Next, the reaction was quenched adding a saturated solution of $NaHCO_3$ (15 mL). The aqueous phase was extracted with

CH_2Cl_2 (3×30 mL), and the organic phases were combined, dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The reaction crude was purified by flash chromatography (20% EtOAc/hexane) affording **3** as a white solid (1.32 g, 70% yield).

Step 3: (S)-6-(3-(benzyloxy)-2-hydroxypropoxy)-5-bromoisobenzofuran-1(3H)-one

[0551] To a solution of **3** (1 eq.) in DMF (5 mL/mmol), 10 eq. of DIPEA and 1.5 eq. of epoxide were added into the flask. The reaction was heated to 100°C. The reaction was monitored by UPLC-MS. Concentrated directly and purify by silica gel chromatography to give **4** (96% yield).

Step 4: (S)-2-((benzyloxy)methyl)-2,3-dihydro-[1,4]dioxino[2,3-f]isobenzofuran-6(8H)-one

[0552] To a solution of **4** (1 eq.) in toluene (5 mL/mmol), $Pd(OAc)_2$ (0.1 eq.), [1,1'-binaphthalen]-2-yldi-tert-butylphosphane (0.1 eq.) and K_3PO_4 (3 eq.) was added into the flask under N_2. The reaction was heated to 140 °C under N_2 for 4h. TLC showed reaction was completed. Quenched with saturated $NaHCO_3$, the organic phase was separated. Ethyl acetate was added to the mixture, the resulting mixture was washed by brine. The combined organic phase was dried by $MgSO_4$. Filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give **5** in (70% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.31 (m, 6H), 6.96 (d, *J* = 1.0 Hz, 1H), 5.21 (d, *J* = 0.9 Hz, 2H), 4.63 (d, *J* = 1.8 Hz, 2H), 4.50 – 4.42 (m, 1H), 4.38 (dd, *J* = 11.6, 2.5 Hz, 1H), 4.22 – 4.11 (m, 1H), 3.79 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.72 (dd, *J* = 10.4, 5.6 Hz, 1H).

Step 5: (S)-2-((benzyloxy)methyl)-7-(hydroxymethyl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid

[0553] To a solution of (S)-2-((benzyloxy)methyl)-2,3-dihydro-[1,4]dioxino[2,3-f]isobenzofuran-6(8H)-one (**5**, 312 mg, 1 mmol, 1 eq.) in tetrahydrofuran (4 mL) and water (4 mL) was added sodium hydroxide (200 mg, 5 eq.). The mixture was stirred at 20 °C for 16 h. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The mixture was adjusted to pH = 5 with aq. hydrochloric acid (1 M) and extracted with ethyl acetate (10 mL x 3). The organic layer was washed with brine (10 x 2 mL) and dried over sodium sulfate. The crude material (**6**) was not further purified and used as crude for the next steps. LC/MS (ESI) m/z: 331.12 (M+H)

Step 6: (2S)-2-((benzyloxy)methyl)-8-hydroxy-2,3-dihydro-[1,4]dioxino[2,3-f]isobenzofuran-6(8H)-one

[0554] To a solution of **6** (1.0 eq., 330 mg) in DCM (10 mL) was added DMP (1.2 eq.) at 0 °C and stirred it for 30 mins. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The reaction mixture was then diluted with DCM, washed with brine, dried over and concentrated

under reduced pressure. The residue was purified by silica gel chromatography to give **7** in (70% yield). LC/MS (ESI) m/z: 346.12 ($M+H_2O$).

Step 7&8: (S)-3-((S)-2-((benzyloxy)methyl)-6-oxo-2,3,6,8-tetrahydro-7H-[1,4]dioxino[2,3-f]isoindol-7-yl)piperidine-2,6-dione

[0555] A mixture of **7** (1.0 eq., 303 mg), (S)-3-aminopiperidine-2,6-dione (1.5 e eq., 199.5 mg) and NaOAc (3.0 eq., 198 mg) was dissolved in methanol:DCM (1:1, 20 mL), and kept stirring at rt for 20 min. Then $NaBH_3CN$ (2.0 eq., 124 mg) was added. 2 h Later, UPLC-MS showed the starting material **7** was completely conversion and a new main peak **8** with desired MS formed. LC/MS (ESI) m/z: 441.16 (M+H). The crude compound **8** (1.0 eq., 440 mg) was dissolved in CH_3CN (4 mL) and was treated with HOAc (15 eq.). The rection was heated at 60 °C and stirred for 2h. Next, the reaction mixture was quenched with water and concentrated under reduced pressure to give a residue which was purified by pre-HPLC to give **I-34** in (70% yield). LC/MS (ESI) m/z: 423.15 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 3.4 Hz, 1H), 7.48 – 7.30 (m, 6H), 6.97 (s, 1H), 5.21 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.62 (s, 2H), 4.48 – 4.31 (m, 3H), 4.24 (dd, *J* = 15.9, 5.6 Hz, 1H), 4.14 (ddd, *J* = 11.6, 7.1, 2.0 Hz, 1H), 3.84 – 3.62 (m, 2H), 2.99 – 2.72 (m, 2H), 2.30 (td, *J* = 12.7, 5.6 Hz, 1H), 2.20 (dq, *J* = 8.0, 4.1, 3.4 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.65, 169.81, 143.89, 137.44, 135.12, 128.55, 128.01, 127.80, 127.77, 124.14, 112.61, 111.68, 73.76, 73.74, 72.59, 72.55, 68.33, 68.30, 65.33, 52.05, 46.79, 31.47, 23.33.

Step 9: (S)-2-((benzyloxy)methyl)-2,3-dihydro-[1,4]dioxino[2,3-f]isobenzofuran-6,8-dione

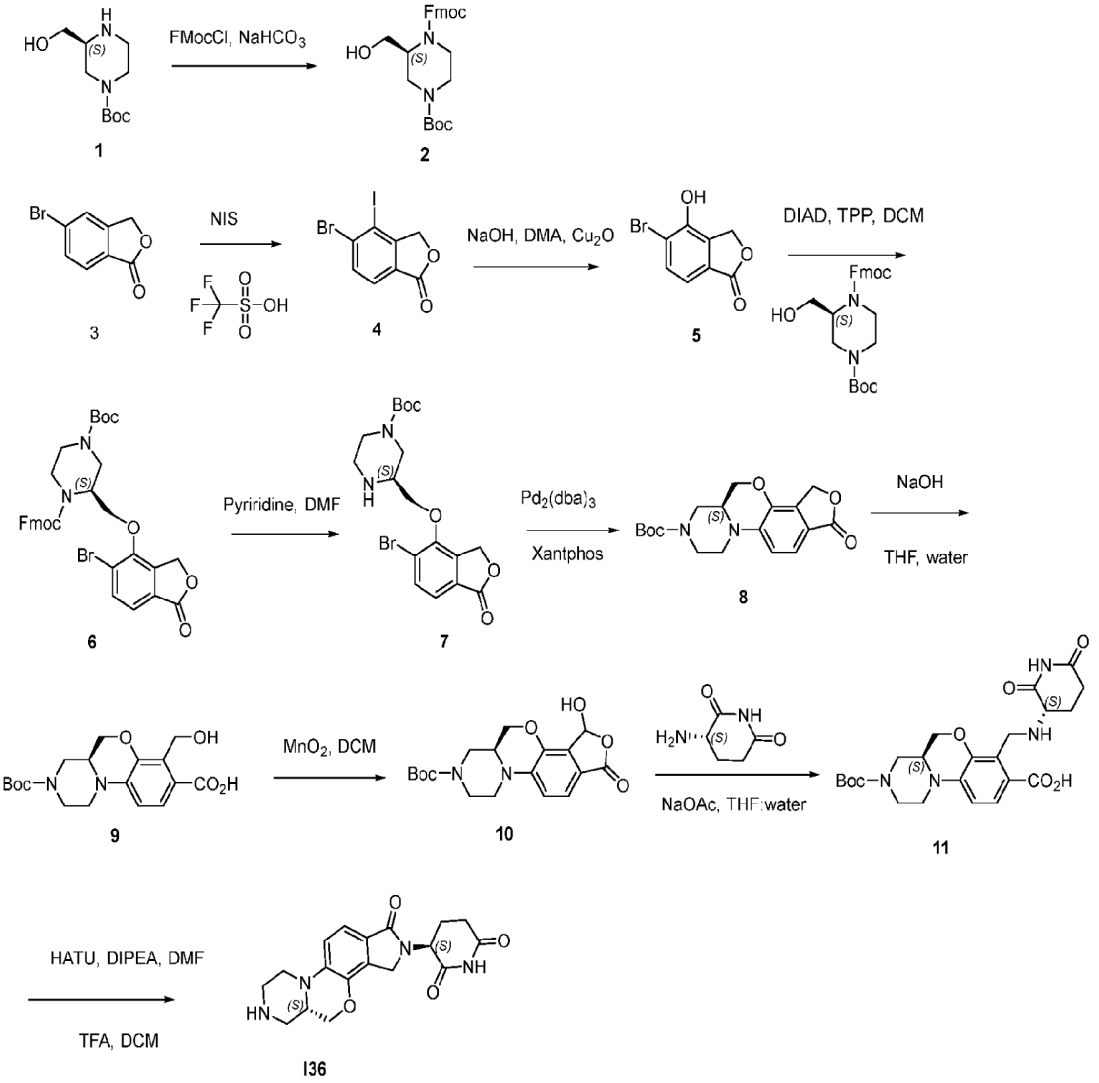
[0556] To a solution of **6** (1.0 eq., 330 mg) in DCM (10 mL) was added DMP (2.0 eq.) at 0 °C and stirred it for 2 h at room temperature. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The reaction mixture was then diluted with DCM, washed with brine, dried over and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **9** in (70% yield). LC/MS (ESI) m/z: 327.10 (M+H).

Step 10: (2S)-2-((benzyloxy)methyl)-7-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-6H-[1,4]dioxino[2,3-f]isoindole-6,8(7H)-dione

[0557] Compound **9** (50 mg, 0.15 mmol) and DIPEA (10 eq.) were dissolved in dry DMF (4 mL), and the reaction mixture was stirred at 60 °C for 2h. TLC showed the reaction was complete. The crude product which was purified by flash chromatography on silica gel (ethyl acetate:hexane= 1:1) to give compound **I-35** in 80% yield. LC/MS (ESI) m/z: 437.15 (M+H). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.97 (s, 1H), 7.46 – 7.30 (m, 7H), 4.95 (dd, *J* = 12.2, 5.3 Hz, 1H), 4.63 (d, *J* =

2.1 Hz, 2H), 4.51 – 4.37 (m, 2H), 4.22 (dd, *J* = 12.0, 7.6 Hz, 1H), 3.85 – 3.68 (m, 2H), 2.98 – 2.69 (m, 3H), 2.23 – 2.08 (m, 1H).

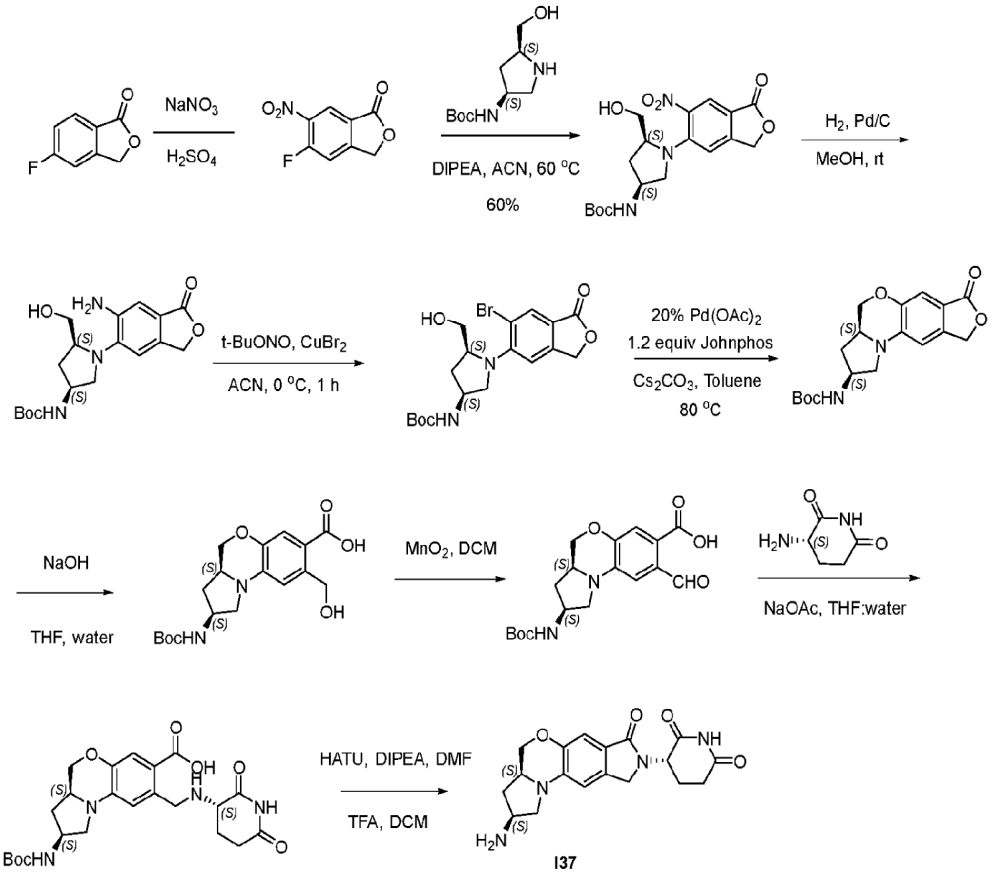
Intermediate 36. (S)-3-((S)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0558] Intermediate **I-36** was made using the similar procedure for making intermediate **I-23.**

[0559] ^{1}H NMR of compound **I-36** (400 MHz, Methanol-d$_4$) δ 7.37 (d, J = 8.3 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 5.11 (ddd, J = 13.3, 5.2, 2.2 Hz, 1H), 4.50 – 4.34 (m, 3H), 4.34 – 4.10 (m, 3H), 3.67 – 3.42 (m, 4H), 3.30 – 3.22 (m, 1H), 3.22 – 3.09 (m, 1H), 3.02 (td, J = 12.2, 5.7 Hz, 1H), 2.91 (ddd, J = 18.5, 13.4, 5.4 Hz, 1H), 2.79 (ddd, J = 17.6, 4.7, 2.4 Hz, 1H), 2.57 – 2.41 (m, 1H), 2.16 (dtd, J = 12.9, 5.3, 2.5 Hz, 1H).

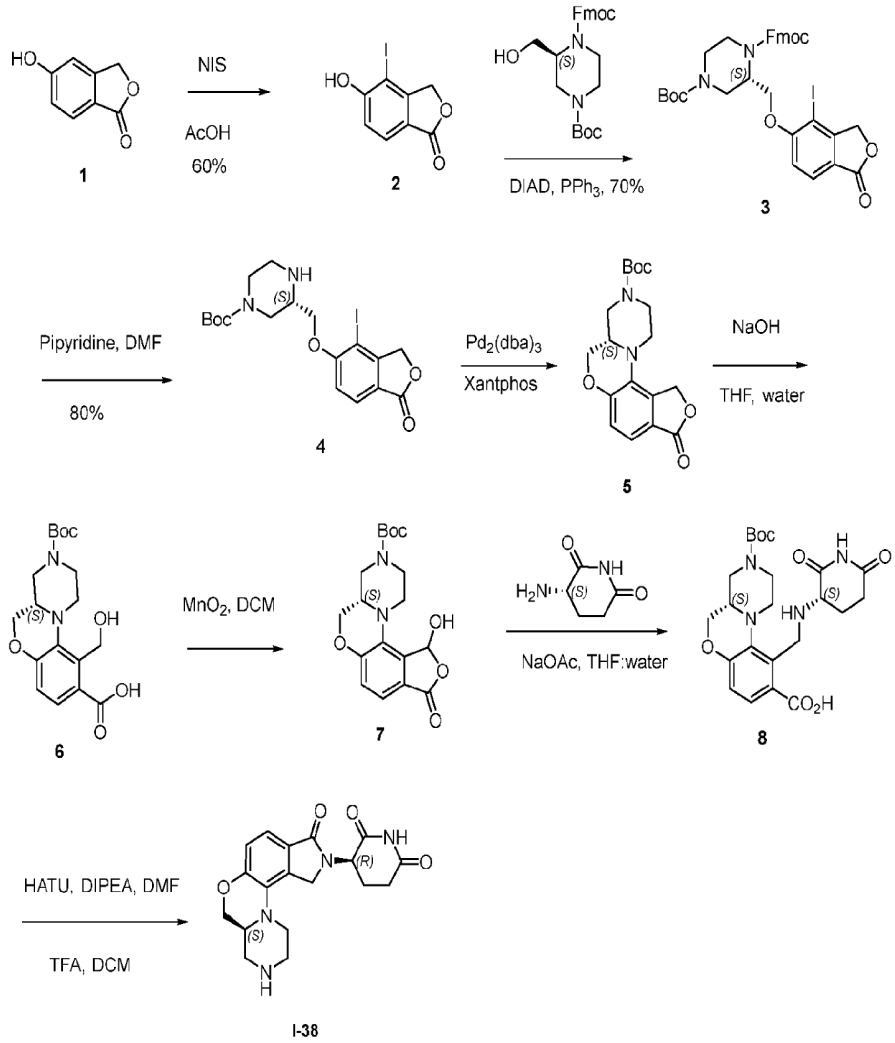
Intermediate 37. (S)-3-((2S,3aS)-2-amino-7-oxo-2,3,3a,4,7,9-hexahydro-1H,8H-pyrrolo[1',2':4,5][1,4]oxazino[2,3-f]isoindol-8-yl)piperidine-2,6-dione



[0560] Intermediate **I-37** was made using the similar procedure for making intermediate **I-24.**

[0561] ^{1}H NMR of compound **I-37** (400 MHz, Methanol-d4) d 7.16 (s, 1H), 6.72 (s, 1H), 5.09 (dt, J = 13.3, 5.1 Hz, 1H), 4.58 (d, J = 7.1 Hz, 2H), 4.36 (d, J = 6.7 Hz, 2H), 4.15 (d, J = 3.6 Hz, 1H), 3.79 (dd, J = 10.4, 7.9 Hz, 1H), 3.72 – 3.62 (m, 2H), 3.53 – 3.40 (m, 1H), 2.96 – 2.84 (m, 1H), 2.78 (ddd, J = 17.4, 4.8, 2.5 Hz, 1H), 2.61 (ddd, J = 12.5, 8.6, 4.1 Hz, 1H), 2.55 – 2.37 (m, 1H), 2.16 (ddq, J = 10.4, 5.3, 2.7 Hz, 1H), 1.79 – 1.59 (m, 1H).

Intermediate 38. (R)-3-((S)-3-oxo-1,3,7,7a,8,9,10,11-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[3,2-e]isoindol-2-yl)piperidine-2,6-dione

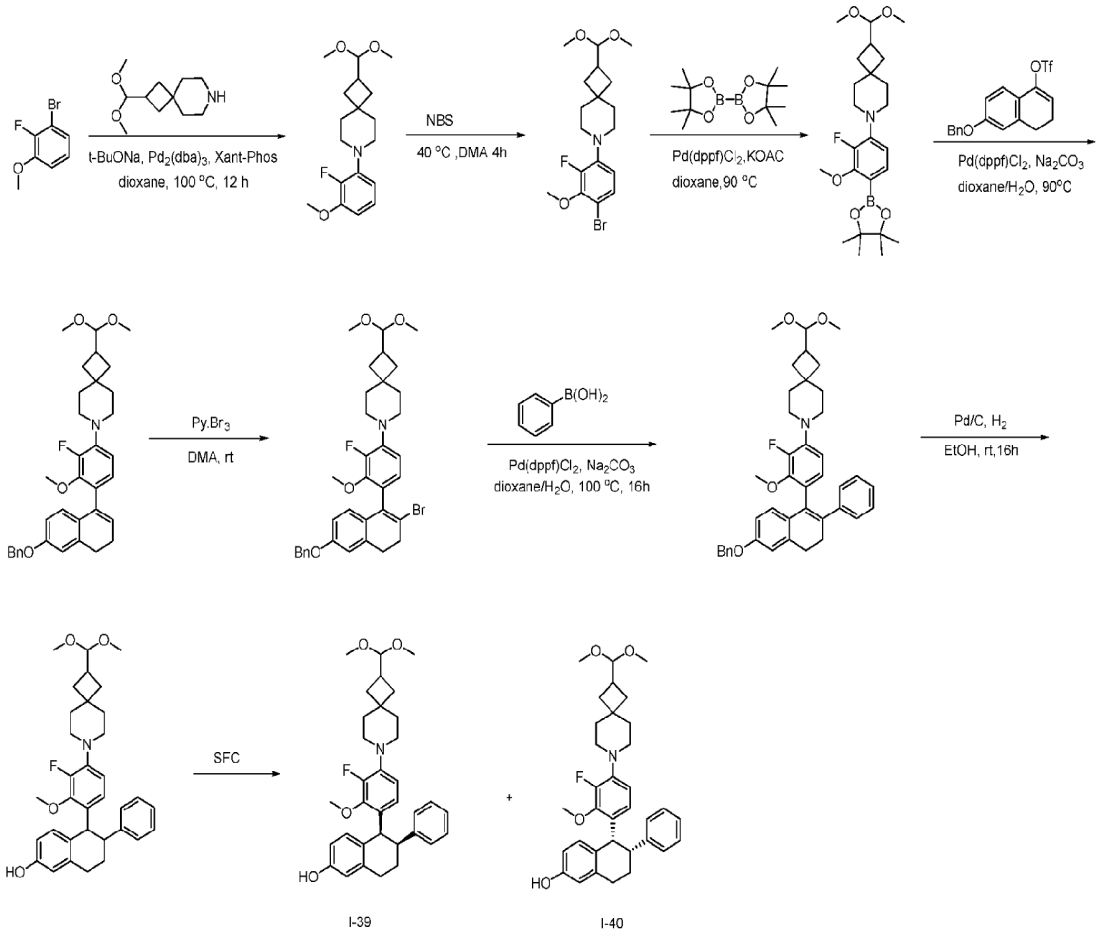


[0562] Intermediate **I-38** was made using the similar procedure for making intermediate **I-23.**

[0563] ^{1}H NMR of compound **I-38** (400 MHz, Methanol-d_4) δ 7.32 (d, J = 8.1 Hz, 1H), 7.02 (dd, J = 8.1, 0.9 Hz, 1H), 5.15 (dd, J = 13.4, 5.2 Hz, 1H), 4.70 – 4.47 (m, 2H), 4.34 (ddd, J = 11.3, 4.2, 2.8 Hz, 1H), 4.14 (ddd, J = 11.3, 9.8, 7.2 Hz, 1H), 4.04 – 3.91 (m, 1H), 3.65 (ddq, J = 10.4, 7.1, 3.4, 2.8 Hz, 1H), 3.54 – 3.39 (m, 2H), 3.30 – 3.22 (m, 2H), 3.14 (dt, J = 12.8, 10.6 Hz, 1H), 2.94 (ddd, J = 17.6, 13.5, 5.4 Hz, 1H), 2.80 (ddd, J = 17.6, 4.7, 2.4 Hz, 1H), 2.60 – 2.42 (m, 1H), 2.19 (ddq, J = 10.5, 5.4, 2.8 Hz, 1H).

Intermediates 39 and 40: (5S,6S)-5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-3-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol & (5R,6R)-5-(4-(2-

(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-3-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol



Step 1: 2-(dimethoxymethyl)-7-(2-fluoro-3-methoxyphenyl)-7-azaspiro[3.5]nonane

[0564] A mixture of 1-bromo-2-fluoro-3-methoxybenzene (7.00 g, 1 eq, 34.1 mmol), $Pd_2(dba)_3$ (1.56 g, 0.05 eq, 1.71 mmol), t-BuONa (3.28 g, 1 eq, 34.1 mmol), 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (7.48 g, 1.1 eq, 37.6 mmol), xantphos (1.98 g, 0.1 eq, 3.41 mmol) in 1,4-Dioxane (70.0 mL) was purged with nitrogen and heated to 100 °C for 16h. TLC showed the reaction was complete. The mixture was diluted with ethyl acetate (50 mL) and washed with water (50 mL). The organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by silica gel column chromatography using 0-50% EtOAc/hexane to give 2-(dimethoxymethyl)-7-(2-fluoro-3-methoxyphenyl)-7-azaspiro[3.5]nonane (2.20 g, 19.9 %), LC-MS (ESI, m/z): mass calcd. For $C_{18}H_{26}FNO_3$, 323.4; found,324.1 $[M+H]^+$.

Step 2: 7-(4-bromo-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0565] To a mixture of 2-(dimethoxymethyl)-7-(2-fluoro-3-methoxyphenyl)-7-azaspiro[3.5]nonane (2.80 g, 1 eq, 8.66 mmol) in DMA (30.0 mL)was added NBS (1.46 g, 0.95 eq, 8.22 mmol) slowly at 0 °C over 30 minutes. The mixture was stirred at 0 °C for 1 hour. LC-MS showed the reaction was completed. The reaction was added with 10 mL of Sat. NH_4Cl solution, followed by 110 mL of water, then extracted with EtOAc (120 mLx3). The combined organic layers were washed with water (120 mLx2) and brine (120 mL) successively, then dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by silica gel column chromatography using 0-50% EtOAc/hexane to afford 7-(4-bromo-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (2.70 g, 77.5 %) as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{18}H_{25}BrFNO_3$, 401.30; found, 402.0 $[M+H]^+$.

Step 3: 2-(dimethoxymethyl)-7-(2-fluoro-3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7-azaspiro[3.5]nonane

[0566] To a mixture of 7-(4-bromo-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.00 g, 1 eq, 2.49 mmol), Bis(pinacolato)diboron (1.26 g, 2 eq, 4.97 mmol) in 1,4-Dioxane (10.0 mL) was added $PdCl_2$(dppf) (182 mg, 0.1 eq, 249 μmol) and KOAC (732 mg, 3 eq, 7.46 mmol). The mixture was stirred at 90 °C for 16 hours under Ar, then cooled to rt and diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic phase was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford 2-(dimethoxymethyl)-7-(2-fluoro-3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7-azaspiro[3.5]nonane (600 mg, 53.7 %) as a white solid. LC-MS (ESI, m/z): mass calcd. For $C_{24}H_{37}BFNO_5$, 449.3; found, 450.4 $[M+H]^+$.

Step 4: 7-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0567] To a mixture of 2-(dimethoxymethyl)-7-(2-fluoro-3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-7-azaspiro[3.5]nonane (200 mg, 1 eq, 445 μmol), 6-(benzyloxy)-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (188 mg, 1.1 eq, 490 μmol), Na_2CO_3 (94.3 mg, 2 eq, 890 μmol) in 1,4-Dioxane (10.0 mL) and H_2O (1.00 mL) was added $PdCl_2$(dppf) (32.6 mg, 0.1 eq, 44.5 μmol) and the mixture was stirred at 90 °C for 16 hours under Ar. The mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic phase was

washed with brine (50 mL), then dried over Na_2SO_4 and filtered. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford 7-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (200 mg, 80.6 %) as a white solid. LC-MS (ESI, m/z): mass calcd. For $C_{35}H_{40}FNO_4$, 557.7; found, 558.4 $[M+H]^+$.

Step 5: 7-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0568] To a mixture of 7-(4-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (900 mg, 1 eq, 1.61 mmol) in DMA (10.0 mL) was added $PyBr_3$ (515 mg, 1 eq, 1.61 mmol) slowly at 0 °C over 30 minutes. The mixture was stirred at 0 °C for 1 hour. LC-MS showed the reaction was completed. 10 mL of Sat. NH4Cl solution was added, followed by 110 mL of water, and the resulting mixture was extracted with EtOAc (120 mLx3). The combined organic layers were washed with water (120 mLx2) and brine (120 mL) successively, then dried over Na_2SO_4, filtered. The filtrate was evaporated to afford 7-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.00 g, 1.57 mmol, 97.3 %) as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{35}H_{39}BrFNO_4$, 635.3; found, 636.4 $[M+H]^+$.

Step 6: 7-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0569] A mixture of 7-(4-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.00 g, 1 eq, 1.57 mmol), phenylboronic acid (383 mg, 2 eq, 3.14 mmol), Na_2CO_3 (333 mg, 2 eq, 3.14 mmol), $PdCl_2$(dppf) (115 mg, 0.1 eq, 157 μmol) in1,4-dioxane (10.0 mL) and H_2O (2.00 mL) was stirred at 100 °C for 16 hours under Ar. The mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic phase was washed with brine (50 mL), then dried over Na_2SO_4 and filtered. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford 7-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (500 mg, 50.2 %)as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{41}H_{44}FNO_4$, 633.8; found, 634.4 $[M+H]^+$.

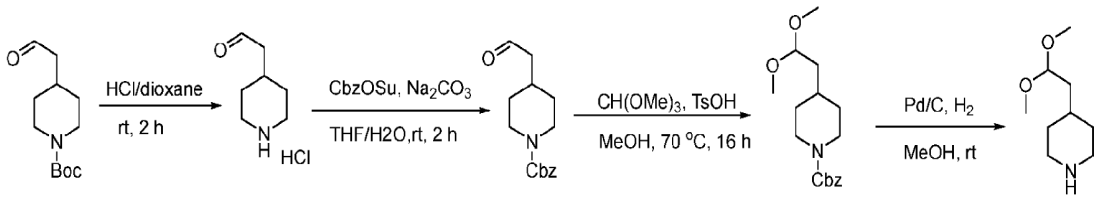
Step 7: 5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-3-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

[0570] A mixture of 7-(4-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)-2-fluoro-3-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (400 mg, 1 eq, 631 µmol), Pd/C (67 mg, 10% on Carbon, wetted with ca. 55% water) in MeOH (10.0 mL) was heated to 40 °C for 16 hours under H_2 atmosphere (1 atm). LC-MS showed the reaction was completed. The reaction mixture was cooled to room temperature, filtered. The filter cake was washed with EtOAc (20 mLx2). The filtrate was evaporated and the residue purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to to afford 5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-3-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (200 mg, 367 µmol, 58.1 %) as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{34}H_{40}FNO_4$, 545.29; found, 546.4 $[M+H]^+$.

Step 8 : (5S,6S)-5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-3-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol & (5R,6R)-5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-3-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

[0571] The tert-butyl 5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-3-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (200 mg) was separated by SFC to afford compound (5S,6S)-5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-3-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (80 mg) as a white solid and (5R,6R)-5-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-3-fluoro-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (80 mg) as a white solid. LC-MS (ESI, m/z): mass calcd. For $C_{34}H_{40}FNO_4$, 545.29; found, 546.4 $[M+H]^+$.

Intermediate 41: 4-(2,2-dimethoxyethyl)piperidine



I-41

Step 1: 2-(piperidin-4-yl)acetaldehyde hydrochloride

[0572] A solution of tert-butyl 4-formylpiperidine-1-carboxylate (3.00 g, 13.2 mmol, 1 eq) in HCl/dioxane (15 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford 2-(piperidin-4-yl)acetaldehyde hydrochloride (2.4 g, crude) as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_7H_{13}NO$, 127.1; found, 128.3 $[M+H]^+$.

Step 2: benzyl 4-(2-oxoethyl)piperidine-1-carboxylate

[0573] To a mixture of 2-(piperidin-4-yl)acetaldehyde hydrochloride (2.4 g, 1 eq, 14.7 mmol) in THF (10 mL) and H_2O (5 mL) was added Na_2CO_3 (7.8 g, 5 eq, 73.6 mmol), CbzOSu (4.4 g, 1.2 eq, 17.7 mmol). The mixture was stirred at room temperature for 1 hour. The reaction solution was diluted with H_2O (20 mL), extracted with EtOAc (20 mLx2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography on silica gel eluting with (PE:EA=2:1) to give benzyl 4-(2-oxoethyl)piperidine-1-carboxylate (2.30 g, 59.9 %) as light yellow oil. LC-MS (ESI, m/z): mass calcd. For $C_{15}H_{19}NO_3$, 261.1; found, 262.2 $[M+H]^+$.

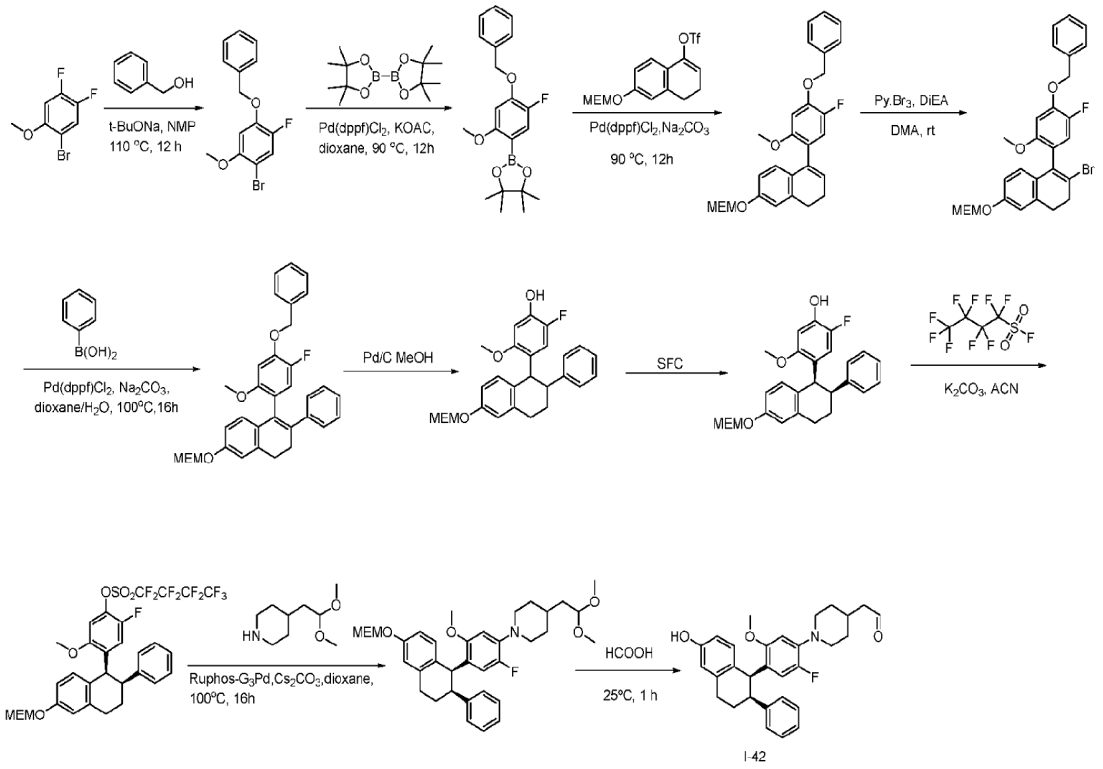
Step 3: benzyl 4-(2,2-dimethoxyethyl)piperidine-1-carboxylate

[0574] To a solution of benzyl 4-(2-oxoethyl)piperidine-1-carboxylate (2.10 g, 1 eq, 8.04 mmol) in MeOH (20 mL) was added $CH(OMe)_3$ (2.56 g, 3 eq, 24.1 mmol) followed by $TsOH{\cdot}H_2O$ (138 mg, 0.1 eq, 804 μmol) and the mixture was stirred at 70 °C for 12 h. The mixture was poured into Na_2CO_3 aqueous solution (20 mL), extracted with EtOAc (20 mLx2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by column chromatography on silica gel eluting with 20% EA in PE to afford benzyl 4-(2,2-dimethoxyethyl)piperidine-1-carboxylate (960 mg, 38.9 %) as light yellow oil. LC-MS (ESI, m/z): mass calcd. For $C_{17}H_{25}NO_4$, 307.2; found, 308.2 $[M+H]^+$.

Step 4: 4-(2,2-dimethoxyethyl)piperidine

[0575] To a solution of compound benzyl 4-(2,2-dimethoxyethyl)piperidine-1-carboxylate (6.30 g, 1 eq, 20.5 mmol) in MeOH (30 mL) was added Pd/C (1.97 g, 10% on Carbon, wetted with ca. 55% water) and the mixture was stirred at room temperature for 16 h under H_2. The mixture was filtered and filtrate was concentrated to give 4-(2,2-dimethoxyethyl)piperidine (3.30 g, 92.9 %) as a white paste. LC-MS (ESI, m/z): mass calcd. For $C_9H_{19}NO_2$, 173.1; found, 174.3 $[M+H]+$.

Intermediate 42: 2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)acetaldehyde



Step 1: 1-(benzyloxy)-4-bromo-2-fluoro-5-methoxybenzene

[0576] To a mixture of 1-bromo-4,5-difluoro-2-methoxybenzene (55.1 g, 1 eq, 247.1 mmol), phenylmethanol (29.4 g, 1.1 eq, 271.8 mmol) in NMP (200 mL) was added sodium tert-butoxide (28.5 g, 1.2 eq, 296.5 mmol). The reaction solution was stirred at 110°C for 4h under N_2. The reaction solution was quenched with NH_4Cl solution (1M, 300 mL), extracted with EA (400 mL×2). The combined organic layer was washed with brine (300 mL×3), dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated in vacuum. The residue was purified by column chromatography on silica gel eluted with (EA/PE=1:10) to give 1-(benzyloxy)-4-bromo-2-fluoro-5-methoxybenzene (65.0 g, 84.86 %) as yellow oil. LC-MS (ESI, m/z): mass calcd. For $C_{15}H_{14}BrFO_2$, 310.0; found, 311.1 $[M+H]^+$.

Step 2: 2-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[0577] To a mixture of 1-(benzyloxy)-4-bromo-2-fluoro-5-methoxybenzene (65.52 g, 1 eq, 210.6 mmol), bis(pinacolato)diboron (80.21 g, 1.5 eq, 315.9 mmol), potassium acetate (41.33 g, 2 eq, 421.1 mmol) in 1,4-dioxane (300 mL) was added $Pd(dppf)Cl_2$ (3.1 g, 0.02 eq, 4.21 mmol) and the mixture was stirred at 100°C for 12 h under N_2. The reaction solution was diluted with H_2O (300 mL), extracted with EA (200 mL×2). The combined organic layer was washed with brine(200mL×3), dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated in vacuum.

The residue was purified by column chromatography on silica gel eluted with (PE: EA=10:1) to give 2-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (33.9 g, 44.9 %) as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{20}H_{24}BFO_4$, 358.2; found, 359.4 $[M+H]^+$.

Step 3: 4-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-7-((2-methoxyethoxy)methoxy)-1,2-dihydronaphthalene

[0578] To a mixture of 2-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.50 g, 1 eq, 9.77 mmol), 6-((2-methoxyethoxy)methoxy)-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (4.48 g, 1.2 eq, 11.7 mmol), Na_2CO_3 (2.07 g, 2 eq, 19.5 mmol) in 1,4-dioxane (35.0 mL)/H_2O (2.0 mL) was added $Pd(dppf)Cl_2$ (0.36 g, 0.05 eq, 488 μmol) and the mixture was stirred at 90°C for 12 hours under N_2. The mixture was poured into H_2O (30 mL), extracted with EtOAc (20 mLx2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography on silica gel eluted with (PE:EA=5:1) to give 4-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-7-((2-methoxyethoxy)methoxy)-1,2-dihydronaphthalene (1.70 g, 37.5 %) as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{28}H_{29}FO_5$, 464.2; found, 465.3 $[M+H]^+$.

Step 4: 4-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-3-bromo-7-((2-methoxyethoxy)methoxy)-1,2-dihydronaphthalene

[0579] To a mixture of 4-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-7-((2-methoxyethoxy)methoxy)-1,2-dihydronaphthalene (1.6 g, 3.5 mmol, 1 eq.) and DIEA (0.89 g, 6.9 mmol, 2 eq.) in DMA (10 mL), was added pyridinium tribromide (1.3 g, 4.2 mmol, 1.2 eq.) at 0°C. The mixture was stirred at room temperature for 3h. The mixture was poured into H_2O (50 mL) and extracted with EtOAc (20 mLx2). The combined organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluted with 0-20% EtOAc/hexane to afford 4-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-3-bromo-7-((2-methoxyethoxy)methoxy)-1,2-dihydronaphthalene (1.5 g, 2.77 mmol, 791%) as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{28}H_{28}BrFO_5$, 542.1; found, 543.2 $[M+H]^+$.

Step 5: 4-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-7-((2-methoxyethoxy)methoxy)-3-phenyl-1,2-dihydronaphthalene

[0580] To a mixture of 4-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-3-bromo-7-((2-methoxyethoxy)methoxy)-1,2-dihydronaphthalene (21.0 g, 1.0 eq, 38.6 mmol), phenylboronic acid (5.65 g, 1.2 eq, 46.4 mmol) in 1,4-Dioxane (100.0 mL)/H_2O (10.0 mL) was addded Na_2CO_3 (8.19 g, 2.0 eq, 77.3 mmol) and $PdCl_2$(dppf) (1.41 g, 0.05 eq, 1.93 mmol). The reaction was stirred at 100 °C for 16 hours under N_2. The mixture was poured into H_2O (200 mL) and extracted with EtOAc (100 mLx2). The combined organic layer was washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel eluted with 0-30% EtOAc/hexane to afford 4-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-7-((2-methoxyethoxy)methoxy)-3-phenyl-1,2-dihydronaphthalene (17.0 g, 31.4 mmol, 81.4 %) as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{34}H_{33}FO_5$, 540.2; found, 541.4 $[M+H]^+$.

Step 6: 2-fluoro-5-methoxy-4-(6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenol

[0581] To a mixture of 4-(4-(benzyloxy)-5-fluoro-2-methoxyphenyl)-7-((2-methoxyethoxy)methoxy)-3-phenyl-1,2-dihydronaphthalene (17.0 g, 1 eq, 31.4 mmol) in MeOH (200 mL) was added Pd/C (5 g, 10% on Carbon, wetted with c.a.55% water).The mixture was stirred at room temperature overnight under H_2. The mixture was filtered and filtrate was concentrated. The residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford 2-fluoro-5-methoxy-4-(6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenol (7.8 g，17.3 mmol, 55%) as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{27}H_{29}FO_5$, 452.2; found, 453.3 $[M+H]^+$.

[0582] 2-fluoro-5-methoxy-4-(6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenol (7.8 g) was purified by SFC to afford 2-fluoro-5-methoxy-4-((1R,2R)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (3.5 g) as yellow solid and 2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (3.5 g) as yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{27}H_{29}FO_5$, 452.2; found, 453.3 $[M+H]^+$.

Step 8: 2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate

[0583] To a mixture of 2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenol (0.50 g, 1 eq, 1.1 mmol) in MeCN (10.0

mL) was added K_2CO_3 (0.31 g, 2 eq, 2.2 mmol), 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (0.43 g, 1.3 eq, 1.4 mmol) at 0°C. The mixture was stirred at room temperature for 16 hours. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with (PE:EA=5:1) to afford 2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (0.81 g, 100 %) as yellow oil. LC-MS (ESI, m/z): mass calcd. For $C_{31}H_{28}F_{10}O_7S$, 734.1; found, 735.2 $[M+H]^+$.

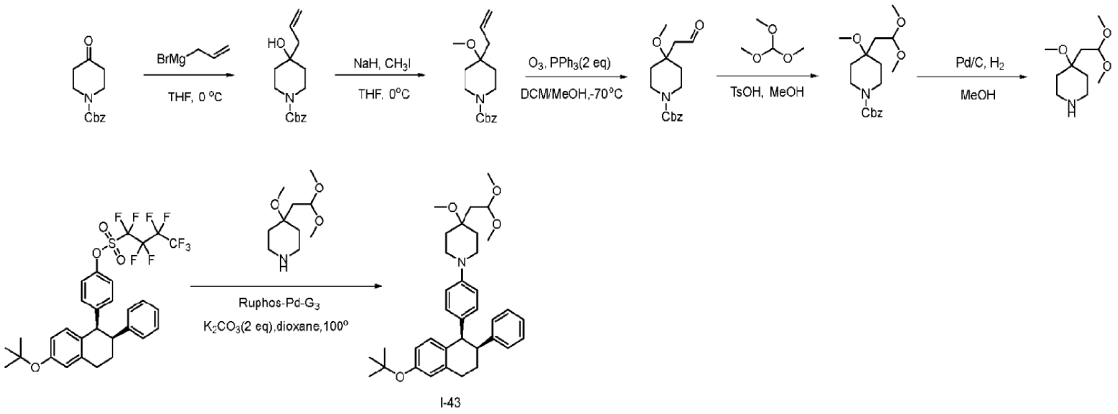
Step 9: 4-(2,2-dimethoxyethyl)-1-(2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine

[0584] To a mixture of 2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (0.50 g, 1 eq, 0.68 mmol), 4-(2,2-dimethoxyethyl)piperidine (0.14 g, 1.2 eq, 0.82 mmol), Cs_2CO_3 (0.44 g, 2 eq, 0.68 mmol) in 1,4-dioxane (10.0 mL)was added RuPhos-Pd-G_3 (57 mg, 0.1 eq, 0.068 mmol). The mixture was stirred at 100°C for 16 h. The mixture was poured into H_2O (50 mL), extracted with EtOAc (20 mLx2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by column chromatography on silica gel using 0-30% EtOAc/hexane to afford 4-(2,2-dimethoxyethyl)-1-(2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine (0.15 g, 0.25 mmol, 36 %) as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{36}H_{46}FNO_6$, 607.3; found, 608.4 $[M+H]^+$.

Step 10: 2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)acetaldehyde

[0585] To a mixture of 4-(2,2-dimethoxyethyl)-1-(2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidine (0.03 g, 1 eq, 0.05 mmol) in HCOOH (2.00 mL). The mixture was stirred at room temperature for 1 h, the mixture was concentrated to afford 2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)acetaldehyde (30.0 mg, crude) as yellow oil. LC-MS (ESI, m/z): mass calcd. For $C_{30}H_{32}FNO_3$, 473.2; found, 474.3 $[M+H]^+$.

Intermediate 43 : 1-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-4-(2,2-dimethoxyethyl)-4-methoxypiperidine



Step 1: benzyl 4-allyl-4-hydroxypiperidine-1-carboxylate

[0586] To a mixture of allylmagnesium bromide (171.4 mL, 1 M in THF, 2 eq, 171.4 mmol) in THF (120.0 mL) at 0°C was added benzyl 4-oxopiperidine-1-carboxylate (20.00 g, 1 eq, 85.8 mmol) in THF (40.0 mL) dropwise slowly at 0 °C over 30 minutes. The mixture was stirred at 0 °C for 5 hours, then quenched with Sat. NH_4Cl solution (40 mL) and water (200 mL), extracted with EtOAc (120 mLx3). The combined organic layers were washed with water (100 mLx2) and brine (200 mL) successively, then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by reversed Chem-flash to afford benzyl 4-allyl-4-hydroxypiperidine-1-carboxylate (9.2 g, 39.0 %) as yellow oil. LC-MS (ESI, m/z): mass calcd. For $C_{16}H_{21}NO_3$, 275.15; found, 276.3 $[M+H]^+$

Step 2: benzyl 4-allyl-4-methoxypiperidine-1-carboxylate

[0587] To a mixture of benzyl 4-allyl-4-hydroxypiperidine-1-carboxylate (7.00 g, 1 eq, 25.4 mmol) in THF (40.0 mL) was added sodium hydride (3.05 g, 60% wt, 3 eq, 76.3 mmol) slowly at 0 °C under N_2. The mixture was stirred for 1.5 hours, then added with iodomethane (5.41 g, 1.5 eq, 38.1 mmol) dropwise slowly at 0 °C. The resulting mixture was stirred at rt for 6 hours, then quenched with Sat. NH_4Cl solution (50 mL) and water (50 mL), extracted with EtOAc (100 mLx3). The combined organic layers were washed with water (60 mLx2) and brine (100 mL) successively, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluted with (PE:EtOAc=5:1) to afford benzyl 4-allyl-4-methoxypiperidine-1-carboxylate (6.80 g, 23.5 mmol, 92.4 %) as a white oil. LC-MS (ESI, m/z): mass calcd. For $C_{17}H_{23}NO_3$, 289.17; found, 290.2 $[M+H]^+$

Step 3: benzyl 4-methoxy-4-(2-oxoethyl)piperidine-1-carboxylate

[0588] An ozone-enriched steam of oxygen was bubbled through the solution of benzyl 4-allyl-4-

methoxypiperidine-1-carboxylate (6.80 g, 1 eq, 23.5 mmol) in DCM (32.0 mL) and MeOH (6.00 mL) at -40°C, until the solution became light blue. Then the solution was purged with argon at -40°C for 10 minutes to remove excess O_3, then added with triphenylphosphane (6.16 g, 1 eq, 23.5 mmol) slowly at -20°C. The resulting mixture was stirred at 25 °C for 1 hour, then poured into ice water (100 mL), extracted with EtOAc (100 mL x 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel eluted with (PE:EtOAc=5:1) to afford benzyl 4-methoxy-4-(2-oxoethyl)piperidine-1-carboxylate (5.00 g, 17.2 mmol, 73.0 %) as a yellow oil. LC-MS (ESI, m/z): mass calcd. For $C_{16}H_{21}NO_4$, 291.15; found, 292.2 $[M+H]^+$.

Step 4: benzyl 4-(2,2-dimethoxyethyl)-4-methoxypiperidine-1-carboxylate

[0589] A mixture of benzyl 4-methoxy-4-(2-oxoethyl)piperidine-1-carboxylate (5.00 g, 1 eq, 17.2 mmol), trimethoxymethane (3.64 g, 2 eq, 34.3 mmol) and 4-methylbenzenesulfonic acid hydrate (163 mg, 0.05 eq, 858 μmol) in MeOH (50.0 mL) was stirred at 60 °C for 12 hours. LC-MS showed the reaction was completed. The mixture was poured into ice water (100 mL), extracted with EtOAc (100 mLx2). The organic layer was washed with brine (100 mL), then dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel eluted with (PE: EtOAc=5:1) to afford benzyl 4-(2,2-dimethoxyethyl)-4-methoxypiperidine-1-carboxylate (4.50 g, 13.3 mmol, 77.7 %) as a white viscous solid. LC-MS (ESI, m/z): mass calcd. For $C_{18}H_{27}NO_5$, 337.19; found, 338.2 [M+H]+

Step 5: 4-(2,2-dimethoxyethyl)-4-methoxypiperidine

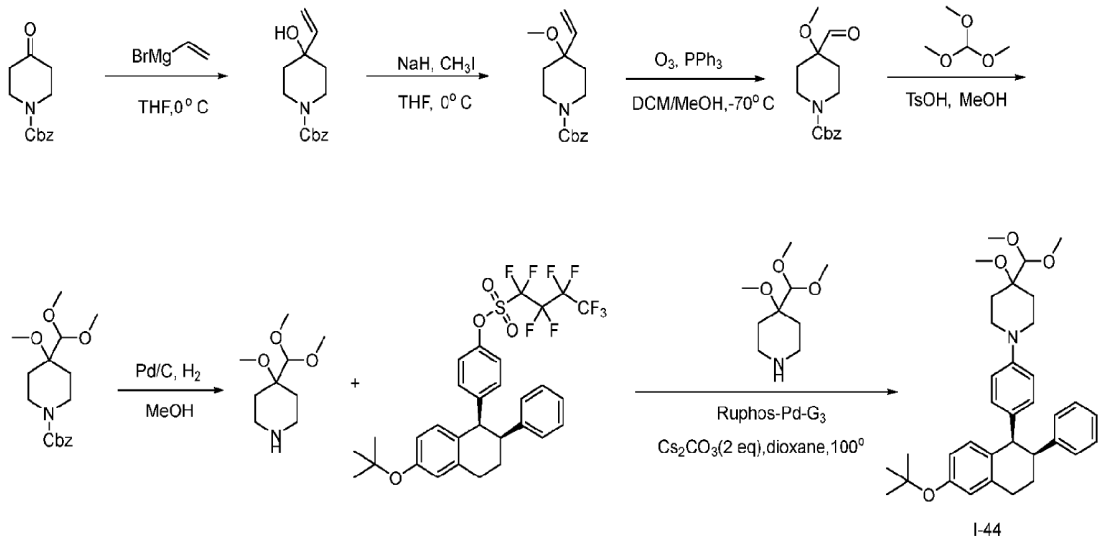
[0590] To a mixture of benzyl 4-(2,2-dimethoxyethyl)-4-methoxypiperidine-1-carboxylate (4.50 g, 1 Eq, 13.3 mmol) in MeOH (50.0 mL) was added Pd/C (946 mg, 10% on Carbon, wetted with ca. 55% water

[0591]). The suspension was degassed and charged with H_2 three times. The mixture was stirred at 25°C for 14 hours. TLC showed was completed. The mixture was filtered and the filtered concentrated under reduced pressure to afford the 4-(2,2-dimethoxyethyl)-4-methoxypiperidine (2.50 g, 12.3 mmol, 92.2 %) as gray oil. LC-MS (ESI, m/z): mass calcd. For $C_{10}H_{21}NO_3$, 203.15; found,204.2 [M+H]+.

Step 6 : 1-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-4-(2,2-dimethoxyethyl)-4-methoxypiperidine

[0592] To a mixture of 4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (0.30 g, 1 eq, 0.46 mmol), 4-(2,2-dimethoxyethyl)-4-methoxypiperidine (0.14 g, 1.5 eq, 0.69 mmol) and K_2CO_3 (63 mg, 1 eq, 0.46 mmol) in 1,4-Dioxane (4.00 mL) was added Ruphos-Pd-G3 (38 mg, 0.1 eq, 46 μmol). The resulting mixture was stirred at 100 °C under N_2 for 12 hours. LCMS showed compound the desired product was formed. The mixture was poured into ice water (10 mL), extracted with EA (20 mL x 2). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel eluted with (PE: EtOAc=5:1) to afford 1-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-4-(2,2-dimethoxyethyl)-4-methoxypiperidine (0.14 g, 55 %) as a white soild. LC-MS (ESI, m/z): mass calcd. For $C_{36}H_{47}NO_4$, 557.35; found, 558.4 [M+H]+

Intermediate 44 : 1-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-4-(dimethoxymethyl)-4-methoxypiperidine



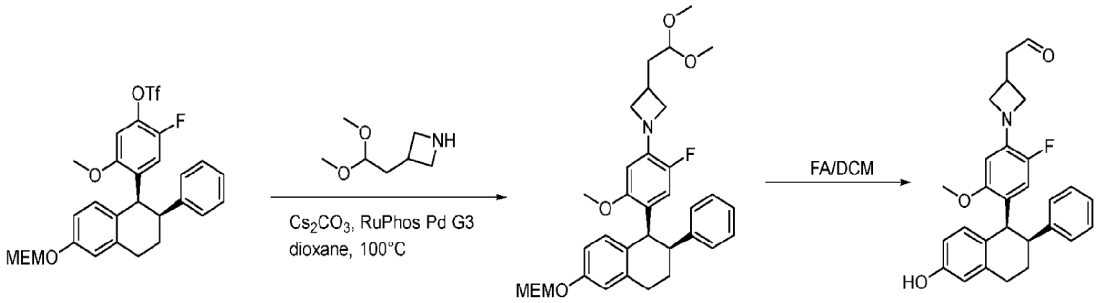
[0593] The synthesis of 4-(dimethoxymethyl)-4-methoxypiperidine is similar to that of 4-(2,2-dimethoxyethyl)-4-methoxypiperidine.

Step 1 : 1-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-4-(dimethoxymethyl)-4-methoxypiperidine

[0594] A mixture of 4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (250 mg, 1 eq, 382 μmol), 4-

(dimethoxymethyl)-4-methoxypiperidine (108 mg, 1.5 Eq, 573 μmol), Cs_2CO_3 (249 mg, 2 eq, 764 μmol) and Ruphos-Pd-G3 (320 mg, 1 eq, 382 μmol) in 1,4-Dioxane (6.00 mL) was stirred at 100 °C under N_2 for 12 hour. LCMS showed compound the desired product was formed. The mixture was poured into ice water (10 mL), extracted with EA (20 mL x 2). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel eluted with (PE:EtOAc=5:1) to afford 1-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-4-(dimethoxymethyl)-4-methoxypiperidine (120 mg, 57.8 %) as a white solid. LC-MS (ESI, m/z): mass calcd. For $C_{35}H_{45}NO_4$, 543.33; found, 544.4 [M+H]+

Intermediate 45: 2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)azetidin-3-yl)acetaldehyde



I-45

Step 1: 3-(2,2-dimethoxyethyl)-1-(2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidine

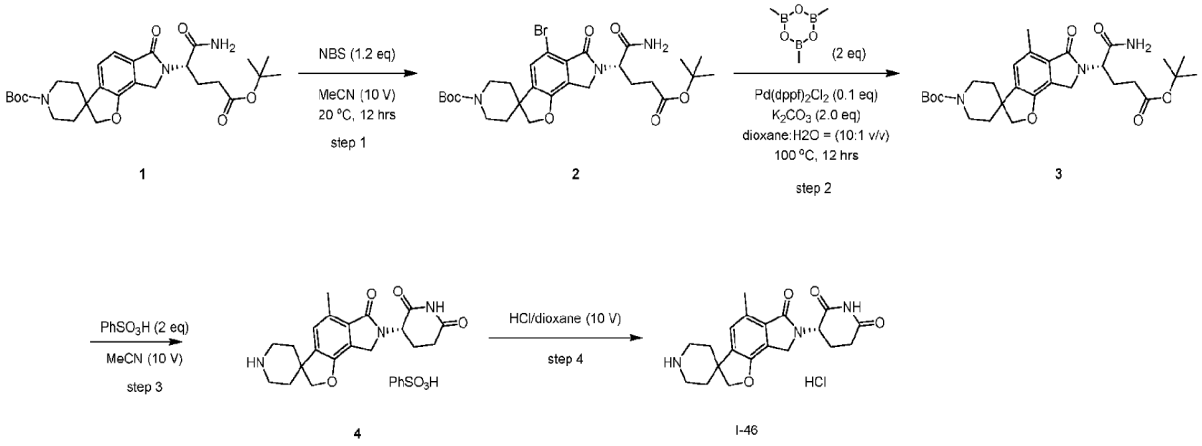
[0595] To a solution of 2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl trifluoromethanesulfonate (639 mg, 1.09 mmol, 1 eq) and 3-(2,2-dimethoxyethyl)azetidine (175 mg, 1.20 mmol, 1.1 eq) in 1,4-Dioxane (10.0 mL) was added Cs_2CO_3 (1.78 g, 5.47 mmol, 5 eq) and RuPhos Pd G3 (7.15 mg, 1.09 mmol, 1 eq). The solution was stirred at 100 °C for 16 hours. The reaction mixture was quenched with addition H_2O (30 mL), and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0~30% Ethyl acetate/Petroleum ether) to afford 3-(2,2-dimethoxyethyl)-1-(2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidine (568 mg,

89.6 %) was obtained as yellow liquid. LC-MS (ESI, m/z): mass calcd. For $C_{34}H_{42}FNO_6$, 579.3; found, 580.1 $[M+H]^+$.

Step 2:2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)azetidin-3-yl)acetaldehyde

[0596] To a solution of 3-(2,2-dimethoxyethyl)-1-(2-fluoro-5-methoxy-4-((1S,2S)-6-((2-methoxyethoxy)methoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)azetidine (568 mg, 980 μmol, 1 eq) in DCM (5.00 mL) was added formic acid (90.2 mg, 1.96 mmol, 2 eq). The solution was stirred at 25 °C for 2 hours. The reaction mixture was quenched with H_2O (5.0 mL x 3), and extracted with DCM (5.0 mL x 3). The combined organic layers were washed with brine (5.0 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0~30% Ethyl acetate/Petroleum ether) to afford 2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)azetidin-3-yl)acetaldehyde (460 mg, 88.0 %) was obtained as a yellow solid. LC-MS (ESI, m/z): mass calcd. For $C_{32}H_{36}FNO_5$, 533.26; found, 534.3 $[M+H]^+$.

Intermediate 46: (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



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Step 1: tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

[0597] To a solution of tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (20 g, 37.8 mmol, 1 eq) in MeCN (200 mL) at 20 °C was added NBS (8.07 g, 45.3 mmol, 1.2 eq) in portions at 10 °C

and the resulting mixture was kept stirring at 20 °C for 12 hrs. TLC analysis (Petroleum ether: Ethyl acetate= 0:1, R_f= 0.51) showed tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate was completely consumed and the mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=100/1, 1/1) to yield tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (18 g, 25.1 mmol, 66.6% yield) was obtained as a yellow solid.

[0598] ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.68 - 8.54 (m, 1H), 7.30 (s, 1H), 6.51 (br s, 1H), 5.68 (br s, 1H), 4.90 (dd, *J* = 6.2, 8.8 Hz, 1H), 4.54 (s, 2H), 4.51 - 4.29 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.87 (br t, *J* = 12.2 Hz, 2H), 2.35 - 2.23 (m, 2H), 2.21 - 2.09 (m, 1H), 1.92 - 1.81 (m, 2H), 1.80 - 1.68 (m, 3H), 1.49 (s, 9H), 1.42 (s, 9H). LC/MS (MH^+): 608.2.

Step 2: tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-methyl-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

[0599] (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (18 g, 29.6 mmol, 1 eq) was dissolved in dioxane (150 mL) and H_2O (15 mL) at 20 °C. To which was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (7.43 g, 59.2 mmol, 8.27 mL, 2 eq), K_2CO_3 (12.3 g, 88.7 mmol, 3 eq) and Pd(dppf)Cl_2 (4.33 g, 5.92 mmol, 0.2 eq) in portions at 20 °C under N_2. The reaction mixture was stirred at 80 °C for 12 hrs under N_2. LCMS showed that (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate was consumed completely and the mixture was diluted with water (100 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=100/1, 1/1) to yield tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-methyl-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate as a yellow solid (9.5 g, 15.7 mmol, 53.2% yield).

[0600] ^{1}H NMR (400 MHz, CDCl3) δ 6.95 (s, 1H), 6.30 (br s, 1H), 5.40 (br s, 1H), 4.94 - 4.79 (m, 1H), 4.49 (s, 2H), 4.43 - 4.28 (m, 2H), 4.16 - 4.08 (m, 2H), 2.88 (br t, J = 12.3 Hz, 2H), 2.64 (s,

3H), 2.43 - 2.20 (m, 3H), 2.18 - 2.08 (m, 1H), 1.94 - 1.81 (m, 2H), 1.72 (br d, J = 13.4 Hz, 2H), 1.50 (s, 8H), 1.42 (s, 8H). LC/MS (MH^+): 544.4.

Step 3: (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione benzenesulfonate

[0601] $PhSO_3H$ (5.24 g, 33.1 mmol, 2 eq) was dissolved in MeCN (100 mL) at 20 °C. To which was add a solution of tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-methyl-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (9 g, 16.6 mmol, 1 eq) in MeCN (50 mL) drop-wise. The reaction mixture was stirred at 100 °C for 12 hrs. Upon the reaction is completed. the mixture was filtered, and the cake was concentrated under reduced pressure. (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione benzenesulfonate (6.6 g, 10.0 mmol, 60.5% yield, $PhSO_3H$) was obtained as a white solid.

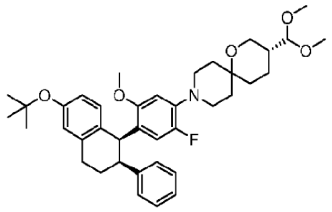
[0602] ^1H NMR: (400 MHz, D_2O) δ 7.75 (br d, J = 6.8 Hz, 2H), 7.58 - 7.40 (m, 3H), 7.19 (s, 1H), 5.14 - 4.96 (m, 1H), 4.59 (s, 2H), 4.48 - 4.27 (m, 2H), 3.48 (br d, J = 13.0 Hz, 2H), 3.12 (br t, J = 12.3 Hz, 2H), 2.98 - 2.77 (m, 2H), 2.53 (s, 3H), 2.48 (br dd, J = 5.4, 13.1 Hz, 1H), 2.25 - 2.05 (m, 3H), 2.01 - 1.90 (m, 2H). LC/MS (MH^+): 370.2.

Step 4: (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione HCl salt

[0603] (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione benzenesulfonate (6.6 g, 12.5 mmol, 1 eq, $PhSO_3H$) was dissolved in HCl/dioxane (60 mL) at 20 °C and the mixture was stirred at 20 °C for 12 hrs. The mixture was filtered, and the cake was washed by MeCN (50 mL x 2) and concentrated under reduced pressure. (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione HCl salt (4.8 g, 10.6 mmol, 85.1% yield) was obtained as a white solid.

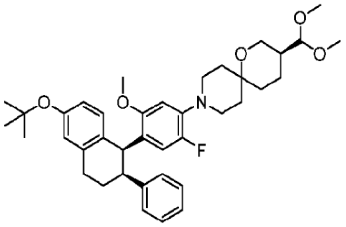
[0604] ^1H NMR (400 MHz, D_2O) δ 7.26 - 7.10 (m, 1H), 5.15 - 5.03 (m, 1H), 4.61 (s, 2H), 4.41 (br d, J = 16.5 Hz, 2H), 3.50 (br d, J = 12.8 Hz, 2H), 3.13 (br t, J = 12.5 Hz, 2H), 2.95 - 2.78 (m, 2H), 2.54 (s, 3H), 2.51 - 2.42 (m, 1H), 2.26 - 2.09 (m, 3H), 2.04 - 1.94 (m, 2H).

Intermediate 47: (R)-9-(4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane



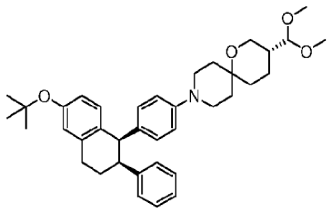
[0605] To a solution of 4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (1.50 g, 1 Eq, 2.13 mmol), (R)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane (636 mg, 1.3 Eq, 2.78 mmol), Xphos (102 mg, 0.1 Eq, 213 μmol) and Cs_2CO_3 (1.39 g, 2 Eq, 4.27 mmol) in dioxane (15 mL) was added $Pd_2(dba)_3$ (196 mg, 0.1 Eq, 213 μmol). The mixture was stirred at 100 °C for 24 hours. TLC (Petroleum ether: Ethyl acetate = 5: 1, R_f= 0.68) indicated 4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate was consumed completely, and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=100/1, 1/1). (R)-9-(4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane (0.80 g, 1.2 mmol, 57% yield) was obtained as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.13 - 7.03 (m, 3H), 6.86 - 6.75 (m, 4H), 6.74 - 6.68 (m, 1H), 6.31 (d, *J* = 13.7 Hz, 1H), 6.13 (d, *J* = 7.5 Hz, 1H), 4.83 (br d, *J* = 5.4 Hz, 1H), 4.17 (d, *J* = 7.5 Hz, 1H), 3.74 (br dd, *J* = 4.0, 12.1 Hz, 1H), 3.49 - 3.40 (m, 1H), 3.34 (d, *J* = 1.5 Hz, 7H), 3.11 - 2.93 (m, 8H), 2.87 - 2.77 (m, 1H), 2.33 - 2.13 (m, 2H), 1.98 - 1.87 (m, 1H), 1.81 - 1.69 (m, 4H), 1.63 - 1.57 (m, 1H), 1.53 - 1.42 (m, 3H), 1.36 (s, 9H). m/z+1= 631.8

Intermediate 48: (S)-9-(4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane



[0606] To a solution of 4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (1.50 g, 1 Eq, 2.13 mmol), (S)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane (636 mg, 1.3 Eq, 2.78 mmol), Xphos (102 mg, 0.1 Eq, 213 μmol) and Cs_2CO_3 (1.39 g, 2 Eq, 4.27 mmol) in dioxane (15 mL) was added $Pd_2(dba)_3$ (196 mg, 0.1 Eq, 213 μmol). The mixture was stirred at 100 °C for 24 hours. TLC (Petroleum ether: Ethyl acetate = 5: 1, R_f = 0.68) indicated 4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate was consumed completely, and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=100/1, 1/1). (S)-9-(4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane (0.70 g, 1.1 mmol, 51% yield) was obtained as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.14 - 7.03 (m, 3H), 6.88 - 6.68 (m, 5H), 6.31 (d, *J* = 13.7 Hz, 1H), 6.12 (d, *J* = 7.5 Hz, 1H), 4.83 (br d, *J* = 5.3 Hz, 1H), 4.19 (d, *J* = 7.5 Hz, 1H), 3.75 (br dd, *J* = 3.7, 12.1 Hz, 1H), 3.47 (dd, *J* = 9.8, 11.7 Hz, 1H), 3.39 - 3.25 (m, 7H), 3.11 - 2.93 (m, 8H), 2.92 - 2.85 (m, 1H), 2.33 - 2.14 (m, 2H), 1.98 - 1.86 (m, 1H), 1.80 - 1.68 (m, 4H), 1.63 - 1.57 (m, 2H), 1.54 - 1.43 (m, 2H), 1.36 (s, 9H). m/z+1=631.8

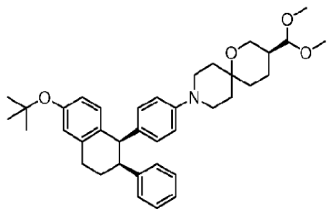
Intermediate 49: (R)-9-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane



[0607] To a solution of 4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (3.00 g, 1 Eq, 4.58 mmol), (R)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane (1.37 g, 1.3 Eq, 5.96 mmol), Xphos (218 mg, 0.1 Eq, 458 μmol) and Cs_2CO_3 (2.99 g, 2 Eq, 9.17 mmol) in dioxane (30 mL) was added $Pd_2(dba)_3$ (420 mg, 0.1 Eq, 458 μmol). The mixture was stirred at 100 °C for 24 hours. TLC (Petroleum ether: Ethyl acetate = 5: 1, R_f = 0.68) indicated 4-((1S,2S)-6-(tert-butoxy)-2-

phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate was consumed completely, and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=100/1, 1/1). (R)-9-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane (1.60 g, 2.7 mmol, 59 %) was obtained as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.21 - 7.09 (m, 3H), 6.89 - 6.77 (m, 4H), 6.73 (dd, *J* = 2.2, 8.3 Hz, 1H), 6.58 (d, *J* = 8.7 Hz, 2H), 6.27 (d, *J* = 8.6 Hz, 2H), 4.23 (br d, *J* = 4.8 Hz, 1H), 4.16 (d, *J* = 7.3 Hz, 1H), 3.72 (br dd, *J* = 4.0, 11.9 Hz, 1H), 3.44 (dd, *J* = 10.1, 11.8 Hz, 1H), 3.38 (br d, *J* = 4.8 Hz, 7H), 3.24 - 3.14 (m, 2H), 3.11 - 2.98 (m, 3H), 2.97 - 2.87 (m, 1H), 2.25 - 2.08 (m, 2H), 1.98 - 1.86 (m, 1H), 1.84 - 1.76 (m, 1H), 1.76 - 1.66 (m, 3H), 1.59 (br d, *J* = 4.5 Hz, 1H), 1.53 - 1.41 (m, 3H), 1.37 (s, 9H). m/z+1= 583.8

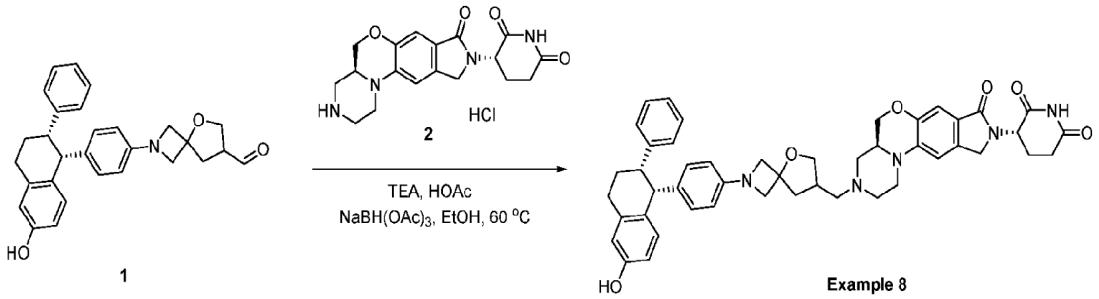
Intermediate 50: (S)-9-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane



[0608] To a solution of 4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (3.50 g, 1 Eq, 5.35 mmol), (S)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane (1.59 g, 1.3 Eq, 6.95 mmol), Xphos (255 mg, 0.1 Eq, 535 µmol) and Cs_2CO_3 (3.48 g, 2 Eq, 10.7 mmol) in dioxane (35 mL) was added $Pd_2(dba)_3$ (490 mg, 0.1 Eq, 535 µmol). The mixture was stirred at 100 °C for 24 hours. TLC (Petroleum ether: Ethyl acetate = 5: 1, R_f= 0.68) indicated 4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate was consumed completely, and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate=100/1, 1/1). (S)-9-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-

1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane (2.00 g, 3.35 mmol, 62.7 % yield) was obtained as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.20 - 7.11 (m, 3H), 6.88 - 6.78 (m, 4H), 6.73 (dd, *J* = 2.3, 8.3 Hz, 1H), 6.58 (d, *J* = 8.7 Hz, 2H), 6.27 (d, *J* = 8.6 Hz, 2H), 4.23 (br d, *J* = 4.8 Hz, 1H), 4.17 (d, *J* = 7.5 Hz, 1H), 3.72 (br dd, *J* = 4.0, 11.7 Hz, 1H), 3.44 (dd, *J* = 10.0, 11.8 Hz, 1H), 3.34 (d, *J* = 1.3 Hz, 7H), 3.25 - 3.13 (m, 2H), 3.09 - 2.99 (m, 3H), 2.93 (dt, *J* = 2.7, 11.6 Hz, 1H), 2.26 - 2.08 (m, 2H), 1.98 - 1.86 (m, 1H), 1.85 - 1.76 (m, 1H), 1.76 - 1.64 (m, 3H), 1.59 (br d, *J* = 4.8 Hz, 1H), 1.55 - 1.41 (m, 4H), 1.37 (s, 9H). m/z+1= 583.8.

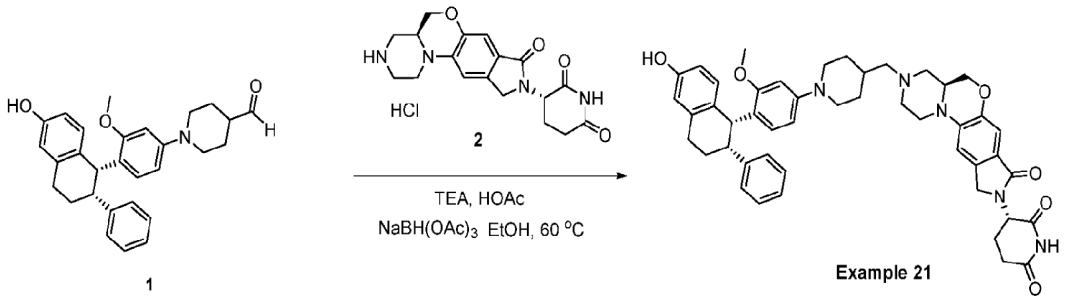
Compound A8. (3R)-3-((4aR)-3-((2-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0609] To a mixture of 2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octane-7-carbaldehyde (30 mg, 0.07 mmol, 1.0 eq) and rac-(R)-3-((R)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride (27 mg, 0.07 mmol, 1.0 eq) in EtOH (5 mL) was added triethylamine (27.5 mg, 0.27 mmol, 4.0 eq), followed by the addition of AcOH (163 mg, 2.72 mmol, 40 eq) and stirred at 25 °C for 0.5 hour. The mixture was added $NaBH(OAc)_3$ (58 mg, 0.27 mmol, 4.0 eq) and stirred at 50 °C for 2 hours. LCMS showed the reaction was completed. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by Prep-HPLC (ACN/ 0.05% FA) to afford (3R)-3-((4aR)-3-((2-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (5.77 mg, 19%) as a white solid. LC-MS purity: 100% (UV at 254 nm), 780.2

$[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.12 (s, 1H), 7.19 – 7.07 (m, 4H), 7.04 – 6.95 (m, 2H), 6.80 (dd, *J* = 16.7, 7.5 Hz, 2H), 6.66 – 6.57 (m, 2H), 6.47 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.31 (d, *J* = 8.3 Hz, 1H), 6.18 (d, *J* = 8.4 Hz, 1H), 6.06 (d, *J* = 8.3 Hz, 1H), 5.03 (dd, *J* = 13.1, 4.9 Hz, 1H), 4.31 (d, *J* = 9.6 Hz, 1H), 4.21 (d, *J* = 22.7 Hz, 2H), 4.15 – 4.10 (m, 1H), 4.00 – 3.87 (m, 3H), 3.87 – 3.71 (m, 3H), 3.70 – 3.60 (m, 2H), 3.59 – 3.49 (m, 3H), 3.03 – 2.76 (m, 6H), 2.71 – 2.58 (m, 3H), 2.44 – 2.29 (m, 3H), 2.09 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.01 – 1.82 (m, 3H), 1.69 (d, *J* = 11.3, 8 Hz, 1H).

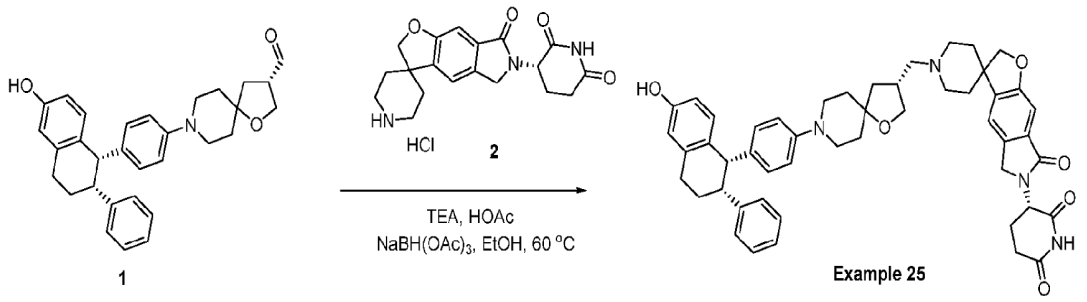
Compound A21. (S)-3-((S)-3-((1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0610] To a mixture of 1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (45.4 mg, 0.10 mmol, 1.0 eq) and (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride (40.4 mg, 0.10 mmol, 1.0 eq) in EtOH (5 mL) was added triethylamine (0.06 mL, 0.41 mmol, 4.0 eq), followed by the addition of AcOH (0.32 mL, 4.11 mmol, 40 eq) and stirred at 25 °C for 0.5 hour. The mixture was added $NaBH(OAc)_3$ (87.2 mg, 0.41 mmol, 4.0 eq) and stirred at 60 °C for 2 hours. LCMS showed the reaction was completed. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by prep-HPLC (ACN/ 0.05% FA) to afford (S)-3-((S)-3-((1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (37.96 mg,47%) as a white solid. LCMS purity: 100% (UV at 254 nm), MS: 782.2 $[M+H]^+$; Retention time R_f = 5.256 min. ^1H NMR (400M Hz, MeOD-d4) *δ* 7.15 (s, 1H), 7.07 (dd, *J* = 7.4, 4.0 Hz,

4H), 6.80–6.73 (m, 2H), 6.67–6.61 (m, 2H), 6.57 (d, *J* = 8.3 Hz, 1H), 6.51 (dd, *J* = 8.3, 2.6 Hz, 2H), 6.28 (s, 1H), 5.51 (s, 1H), 5.10 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.81 (d, *J* = 5.3 Hz, 1H), 4.41–4.27 (m, 3H), 4.03 (dd, *J* = 11.0, 7.9 Hz, 2H), 3.62 (d, *J* = 9.2 Hz, 2H), 3.46 (dd, *J* = 17.5, 12.1 Hz, 2H), 3.26 (d, *J* = 7.3 Hz, 2H), 3.05 (s, 4H), 2.94 (ddd, *J* = 18.3, 15.7, 5.4 Hz, 3H), 2.80 (dd, *J* = 11.9, 7.6 Hz, 3H), 2.68 (s, 2H), 2.53–2.41 (m, 1H), 2.38–2.25 (m, 2H), 2.16 (dd, *J* = 11.2, 6.2 Hz, 1H), 1.95 (t, *J* = 10.1 Hz, 3H), 1.68 (dd, *J* = 15.3, 5.5 Hz, 1H), 1.52–1.42 (m, 2H).

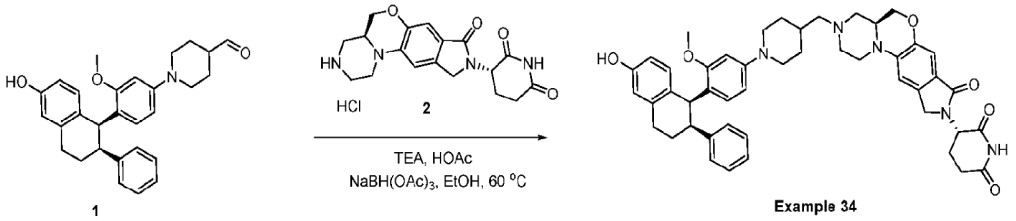
Compound A25. (S)-3-(1'-(((R)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione



[0611] To a mixture of (S)-8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (40 mg, 0.09 mmol, 1.0 eq) and rac-(R)-3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione hydrochloride (32 mg, 0.09 mmol, 1.0 eq) in EtOH (5 mL) was added triethylamine (37 mg, 0.36 mmol, 4.0 eq), followed by the addition of AcOH (219 mg, 3.6 mmol, 40 eq) and stirred at 25 °C for 0.5 hour. The mixture was added $NaBH(OAc)_3$ (77 mg, 0.36 mmol, 4.0 eq) and stirred at 50 °C for 2 hours. LCMS showed the reaction was completed. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by prep-HPLC (ACN/ 0.05% FA) to afford (3S)-3-(1'-((8-(4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (4.9 mg,12%) as a white solid. LC-MS purity: 100% (UV at 254 nm), 807.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 9.13 (s, 1H), 8.19 (s, 1H), 7.46 (s, 1H), 7.13 (t, *J* = 7.6 Hz, 3H), 7.00 (s, 1H), 6.82 (d, *J* = 6.7 Hz, 2H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.59 (s, 1H), 6.53 (d, J = 8.5 Hz, 2H), 6.48 (d, *J* = 8.2 Hz, 1H), 6.20 (d, *J* = 8.5 Hz, 2H), 5.07 (dd, *J* = 13.0, 5.2 Hz, 1H), 4.45 (s, 2H), 4.33 (d, *J* = 16.9 Hz, 1H), 4.20 (d, *J* = 17.0 Hz, 1H), 4.12

(d, *J* = 4.7 Hz, 1H), 3.86 (t, *J* = 7.6 Hz, 1H), 3.46 – 3.41 (m, 3H), 3.02 (s, 4H), 2.98 – 2.78 (m, 6H), 2.64 (d, *J* = 26.2 Hz, 1H), 2.34 (t, *J* = 16.7 Hz, 3H), 2.17 – 2.05 (m, 1H), 1.93 (ddd, *J* = 22.8, 14.6, 8.6 Hz, 6H), 1.71 – 1.57 (m, 6H), 1.33 (dd, *J* = 12.6, 7.2 Hz, 1H).

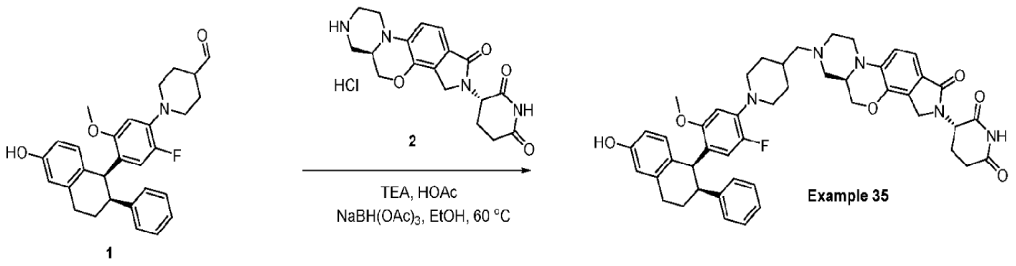
Compound A34. (R)-3-((R)-3-((1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0612] To a mixture of 1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde with structure being tentatively assigned (40 mg, 0.09 mmol, 1.0 eq) and (R)-3-((R)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride (32 mg, 0.09 mmol, 1.0 eq) in EtOH (5 mL) was added triethylamine (37 mg, 0.36 mmol, 4.0 eq), followed by the addition of AcOH (219 mg, 3.64 mmol, 40 eq) and stirred at 25 °C for 0.5 hour. The mixture was added $NaBH(OAc)_3$ (77 mg, 0.36 mmol, 4.0 eq) and stirred at 50 °C for 2 hours. LCMS showed the reaction was completed. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by Prep-HPLC (ACN/ 0.05% FA) to afford (R)-3-((R)-3-((1-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (11.29 mg, 28%) as a white solid. LC-MS purity: 100% (UV at 254 nm), 782.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.06 (s, 1H), 7.22 – 6.92 (m, 5H), 6.73 (d, *J* = 5.8 Hz, 2H), 6.60 – 6.51 (m, 2H), 6.49 – 6.42 (m, 1H), 6.40 – 6.28 (m, 2H), 6.13 (t, *J* = 6.0 Hz, 1H), 5.03 (d, *J* = 13.0 Hz, 1H), 4.65 (d, *J* = 5.2 Hz, 1H), 4.28 – 4.16 (m, 2H), 4.03 – 3.85 (m, 1H), 3.61 (dd, *J* = 21.7, 12.2 Hz, 3H), 3.15 (d, *J* = 35.1 Hz, 4H), 3.00 – 2.85 (m, 8H), 2.63 (d, *J* = 29.1 Hz, 2H), 2.33 (s, 1H), 2.23 – 2.10

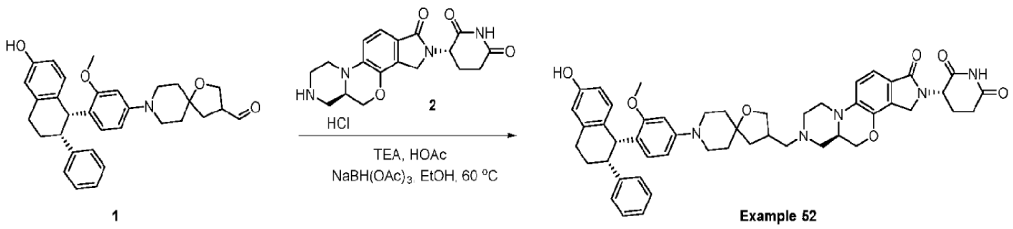
(m, 3H), 1.96 (dd, *J* = 10.7, 5.9 Hz, 2H), 1.85 – 1.73 (m, 3H), 1.58 (dd, *J* = 11.1, 8.2 Hz, 3H), 1.24 (s, 2H).

Compound A35. (S)-3-((S)-7-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-oCtahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



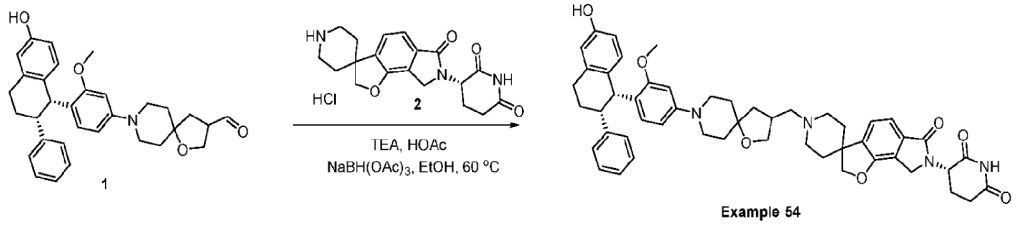
[0613] To a mixture of 1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidine-4-carbaldehyde (19 mg, 0.05 mmol, 1.0 eq) and rac-(R)-3-((S)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride (15 mg, 0.05 mmol, 1.0 eq) in EtOH (5 mL) was added triethylamine (26 mg, 0.2 mmol, 4.0 eq), followed by the addition of AcOH (150 mg, 2 mmol, 40 eq) and stirred at 25 °C for 0.5 hour. The mixture was added $NaBH(OAc)_3$ (59 mg, 0.2 mmol, 4.0 eq) and stirred at 50 °C for 2 hours. LCMS showed the reaction was completed. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by prep-HPLC (ACN/ 0.05% FA) to afford (S)-3-((R)-7-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (5.79 mg,30%) as a white solid. LC-MS purity: 100% (UV at 254 nm), 800.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.32 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 7.1 Hz, 3H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.81 – 6.76 (m, 2H), 6.65 (dd, *J* = 8.2, 5.4 Hz, 2H), 6.54 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.29 (d, *J* = 13.6 Hz, 1H), 6.24 (d, *J* = 7.5 Hz, 1H), 5.10 (dd, *J* = 13.3, 5.0 Hz, 1H), 4.80 (d, *J* = 5.0 Hz, 1H), 4.41 – 4.27 (m, 3H), 4.10 – 4.01 (m, 1H), 3.86 (d, *J* = 12.1 Hz, 1H), 3.19 – 3.05 (m, 2H), 3.01 (d, *J* = 22.5 Hz, 6H), 2.89 (dd, *J* = 13.1, 5.4 Hz, 2H), 2.82 – 2.75 (m, 1H), 2.72 – 2.58 (m, 2H), 2.50 (dd, *J* = 13.2, 4.7 Hz, 1H), 2.35 (d, *J* = 7.0 Hz, 2H), 2.28 (dd, *J* = 22.3, 10.0 Hz, 2H), 2.20 – 2.11 (m, 1H), 1.88 (dd, *J* = 7.6, 3.8 Hz, 3H), 1.73 (dt, *J* = 14.3, 7.0 Hz, 2H), 1.38 (ddd, *J* = 25.5, 18.7, 13.9 Hz, 5H).

Compound A52. (3S)-3-((5aR)-7-((8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0614] To a mixture of 8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (60 mg, 0.14 mmol, 1.0 eq) and rac-(R)-3-((S)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (48.3 mg, 0.14 mmol, 1.0 eq) in EtOH (5 mL) was added triethylamine (55 mg, 0.54 mmol, 4.0 eq), followed by the addition of AcOH (327 mg, 5.4 mmol, 40 eq) and stirred at 25 °C for 0.5 hour. The mixture was added $NaBH(OAc)_3$ (115 mg, 0.54 mmol, 4.0 eq) and stirred at 50 °C for 2 hours. LCMS showed the reaction was completed. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by prep-HPLC (ACN/ 0.05% FA) to afford (3S)-3-((5aR)-7-((8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (18 mg,13%) as a white solid. LC-MS purity: 100% (UV at 254 nm), 800.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.31 (d, J = 8.3 Hz, 1H), 7.05 (dt, J = 12.0, 6.0 Hz, 4H), 6.78 – 6.72 (m, 2H), 6.64 (d, J = 8.3 Hz, 2H), 6.54 – 6.48 (m, 2H), 6.43 (dd, J = 8.5, 2.1 Hz, 1H), 6.21 (d, J = 2.1 Hz, 1H), 5.10 (dd, J = 13.2, 5.1 Hz, 1H), 4.78 (d, J = 5.3 Hz, 1H), 4.40 – 4.34 (m, 2H), 4.05 (dd, J = 12.5, 6.7 Hz, 2H), 3.86 (d, J = 11.8 Hz, 1H), 3.61 (t, J = 8.0 Hz, 1H), 3.23 (s, 1H), 3.15 (s, 3H), 3.03 (s, 3H), 3.00 (d, J = 5.5 Hz, 2H), 2.89 (dd, J = 12.8, 4.9 Hz, 2H), 2.82 – 2.76 (m, 1H), 2.74 – 2.66 (m, 1H), 2.48 (d, J = 7.2 Hz, 2H), 2.30 (s, 1H), 2.20 – 2.05 (m, 3H), 1.89 (d, J = 18.7 Hz, 1H), 1.80 (s, 4H), 1.65 (s, 2H), 1.49 (dd, J = 12.6, 8.3 Hz, 1H), 1.33 (d, J = 18.0 Hz, 5H).

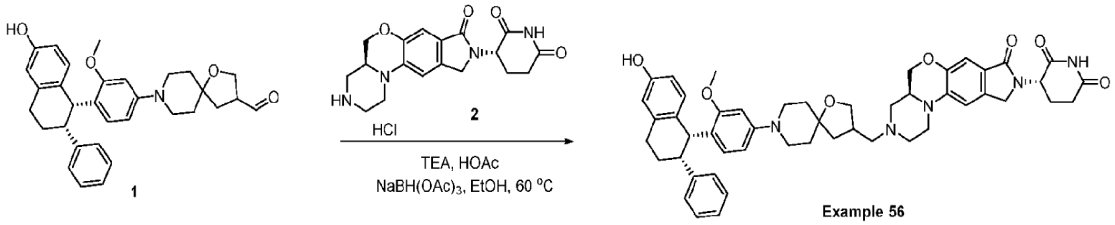
Compound A54. (3S)-3-(1'-((8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0615] To a mixture of 8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (30 mg, 0.06 mmol, 1.0 eq) and (R)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione hydrochloride (23 mg, 0.06 mmol, 1.0 eq) in EtOH (5 mL) was added triethylamine (26 mg, 0.26 mmol, 4.0 eq), followed by the addition of AcOH (154 mg, 2.56 mmol, 40 eq) and stirred at 25 °C for 0.5 hour. The mixture was added $NaBH(OAc)_3$ (54.3 mg, 0.26 mmol, 4.0 eq) and stirred at 50 °C for 2 hours. LCMS showed the reaction was completed. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by Prep-HPLC (ACN/ 0.05% FA) to afford (3S)-3-(1'-((8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (8.4 mg,28%) as a white solid. LC-MS purity: 100% (UV at 254 nm), 837.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.05 (s, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 6.6 Hz, 3H), 6.72 (d, *J* = 9.1 Hz, 2H), 6.56 (d, *J* = 8.5 Hz, 2H), 6.45 (d, *J* = 10.7 Hz, 1H), 6.37 (d, *J* = 8.5 Hz, 1H), 6.31 (d, *J* = 6.3 Hz, 1H), 6.11 (s, 1H), 5.08 (dd, *J* = 12.0, 4.2 Hz, 1H), 4.64 (d, *J* = 5.3 Hz, 1H), 4.52 (s, 2H), 4.37 (d, *J* = 17.0 Hz, 1H), 4.21 (d, *J* = 16.9 Hz, 1H), 3.88 (t, *J* = 7.8 Hz, 1H), 3.47 – 3.42 (m, 1H), 3.20 (dd, *J* = 12.9, 6.6 Hz, 1H), 3.08 (s, 4H), 2.94 (s, 3H), 2.88 (dd, *J* = 19.0, 11.1 Hz, 4H), 2.64 (d, *J* = 25.1 Hz, 2H), 2.34 (d, *J* = 7.0 Hz, 2H), 2.22 – 2.14 (m, 1H), 2.00 (d, *J* = 15.9 Hz, 2H), 1.89 (dd, *J* = 27.6, 14.3 Hz, 4H), 1.71 – 1.64 (m, 4H), 1.60 (d, *J* = 9.6 Hz, 4H), 1.39 – 1.22 (m, 2H).

Compound A56. (3S)-3-((4aS)-3-((8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-

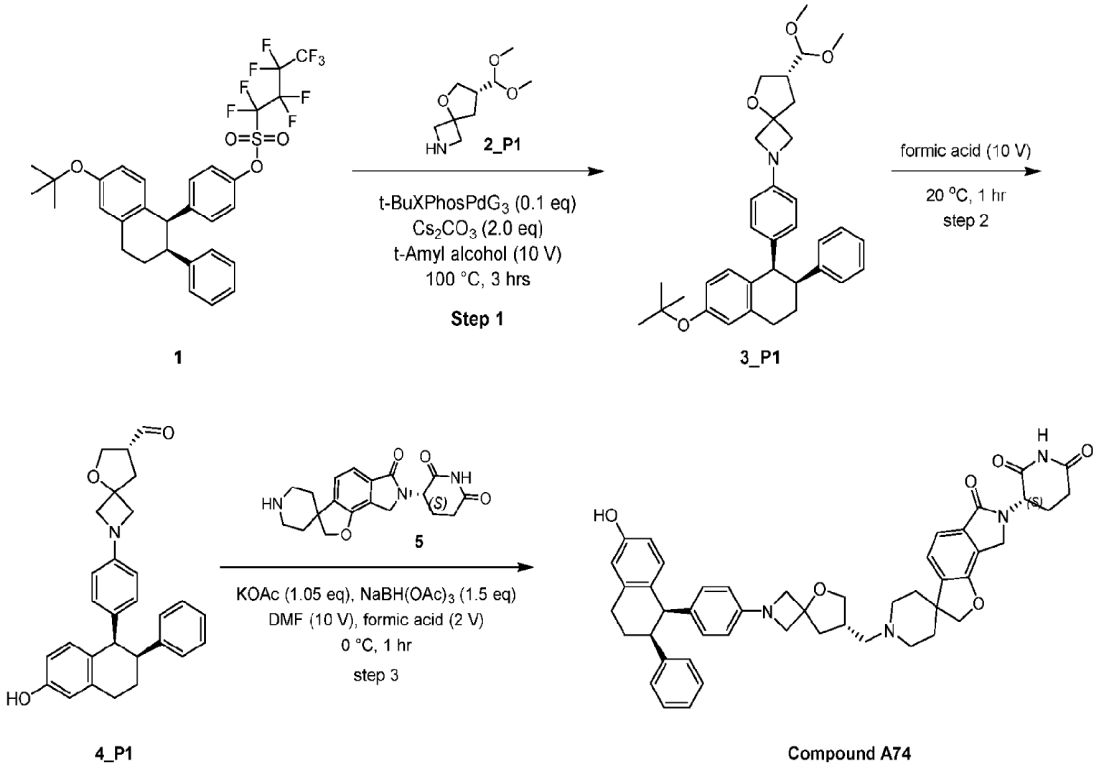
oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

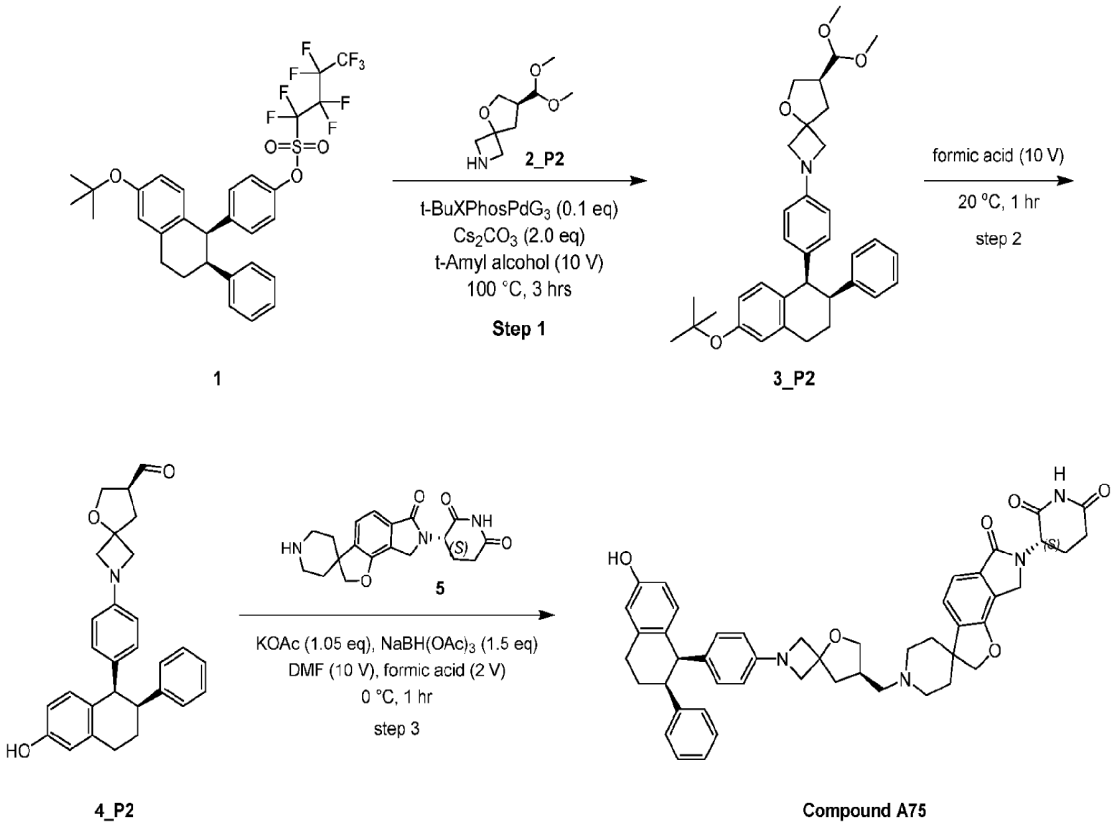


[0616] To a mixture of 8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (60 mg, 0.12 mmol, 1.0 eq) and (R)-3-((R)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride (43 mg, 0.12 mmol, 1.0 eq) in EtOH (5 mL) was added triethylamine (48.6 mg, 0.48 mmol, 4.0 eq), followed by the addition of AcOH (288 mg, 4.11 mmol, 40 eq) and stirred at 25 °C for 0.5 hour. The mixture was added $NaBH(OAc)_3$ (102 mg, 0.48 mmol, 4.0 eq) and stirred at 50 °C for 2 hours. LCMS showed the reaction was completed. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by Prep-HPLC (ACN/ 0.05% FA) to afford (3S)-3-((4aS)-3-((8-(4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (17.43 mg,29%) as a white solid. LC-MS purity: 100% (UV at 254 nm), 838.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.05 (s, 1H), 7.06 (t, J = 5.8 Hz, 4H), 6.93 (s, 1H), 6.74 – 6.70 (m, 2H), 6.55 (d, J = 8.2 Hz, 2H), 6.45 (dd, J = 8.4, 2.5 Hz, 1H), 6.36 (d, J = 8.4 Hz, 1H), 6.31 (d, J = 7.9 Hz, 1H), 6.11 (s, 1H), 5.07 – 4.99 (m, 1H), 4.64 (d, J = 4.9 Hz, 1H), 4.35 – 3.99 (m, 4H), 3.90 (s, 3H), 3.45 (s, 1H), 3.20 (d, J = 14.6 Hz, 2H), 3.08 (s, 4H), 2.94 (s, 3H), 2.67 (d, J = 1.8 Hz, 2H), 2.33 (d, J = 1.8 Hz, 3H), 2.11 (d, J = 28.9 Hz, 3H), 1.96 (d, J = 5.5 Hz, 3H), 1.65 (s, 4H), 1.60 (s, 4H), 1.35 (s, 1H), 1.24 (s, 1H).

Compound A74. (S)-3-((R)-7-(((S)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

Compound A75. (S)-3-((R)-7-(((R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione





Step 1: Synthesis of (R)-2-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-(dimethoxymethyl)-5-oxa-2-azaspiro[3.4]octane

[0617] To the solution of compound **1** (1 g, 1.53 mmol, 1.00 eq) in 2-methyl-2-butanol (10 mL) at 20 °C was add Cs_2CO_3 (995 mg, 3.06 mmol, 2.00 eq) and compound **2_P1** (536 mg, 2.29 mmol, 80% purity, 1.50 eq). t-BuXPhosPdG3 (121 mg, 152 µmol, 0.10 eq) was added to the mixture at 20 °C under N_2 atmosphere. The mixture was stirred at 100 °C for 12 hrs. LCMS showed that the desired product was detected. The mixture was filtered, and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 50:1 to 5:1). The desired product compound **3_P1** (0.63 g, 1.16 mmol) was obtained as yellow oil. m/z (M+1):542.4

Step 2: Synthesis of (R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydro-naphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octane-7-carbaldehyde

[0618] The solution of compound **3_P1** (0.1 g, 184 µmol, 1 eq) in formic acid (2 mL) was stirred at 20 °C for 1 hr. LCMS showed that compound **3_P1** was consumed, and the desired product was

detected. The mixture was concentrated under reduced pressure. The desired product compound **4_P1** (0.08 g, 182. μmol, 98.6% yield) was obtained as a yellow oil. m/z (M+1):440.2

Step 3: Synthesis of (S)-3-(1'-(((S)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

[0619] To the solution of compound **5** (71.3 mg, 182 μmol, 1 eq, HCl) in DMF (2 mL) was add KOAc (18.7 mg, 191 umol, 1.05 eq) at 20 °C. After 10 min, the reaction mixture was cooled to 0 °C, and $NaBH(OAc)_3$ (57.8 mg, 273 umol, 1.5 eq) was added to the mixture; The solution of compound **4_P1** (0.08 g, 182 umol, 1 eq) in formic acid (1 mL) was added at 0 °C, and the mixture was stirred at 0 °C for 1 hr; LCMS showed that compound **4_P1** was consumed and the desired product was detected. The mixture was quenched with water (0.1 mL), and purified by pre-HPLC (column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [water (FA)-ACN]; B%: 30%-60%,8min). The desired product **Compound A74** (75.6 mg, 53.3% yield) was obtained as a white solid.

[0620] ^{1}H NMR (400MHz, DMSO-d6) 10.98 (s, 1H), 9.10 (s, 1H), 7.40 (d, *J*=7.5 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.19 - 7.09 (m, 3H), 6.83 (br d, *J* = 6.7 Hz, 2H), 6.70 - 6.57 (m, 2H), 6.48 (dd, *J* = 2.4, 8.3 Hz, 1H), 6.18 (d, *J* = 8.6 Hz, 2H), 6.06 (d, *J* = 8.6 Hz, 2H), 5.09 (dd, *J* = 5.1, 13.2 Hz, 1H), 4.60 - 4.49 (m, 2H), 4.38 (d, *J* = 17.2 Hz, 1H), 4.22 (d, *J* = 17.2 Hz, 1H), 4.12 (d, *J* = 4.9 Hz, 1H), 3.88 (br t, *J* = 7.6 Hz, 1H), 3.82 - 3.70 (m, 2H), 3.62 (d, *J* = 7.6 Hz, 1H), 3.58 - 3.46 (m, 2H), 3.31 - 3.24 (m, 2H), 3.02 - 2.81 (m, 5H), 2.64 - 2.53 (m, 2H), 2.45 - 2.34 (m, 2H), 2.27 (br dd, *J* = 7.4, 12.5 Hz, 1H), 2.19 - 1.82 (m, 7H), 1.71 (br d, *J* = 10.6 Hz, 3H). m/z (M+1):779.3.

Step 4: Synthesis of (S)-2-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-(dimethoxymethyl)-5-oxa-2-azaspiro[3.4]octane

[0621] To the solution of compound **1** (1 g, 1.53 mmol, 1.00 eq) in 2-methyl-2-butanol (10 mL) was add Cs_2CO_3 (997 mg, 3.06 mmol, 2 eq) and compound **2_P2** (537 mg, 2.30 mmol, 80% purity, 1.5 eq) at 20 °C. t-BuXPhosPdG3 (121 mg, 153 μmol, 0.1 eq) was added to the mixture at 20 °C under N_2 atmosphere, before the mixture was stirred at 100 °C for 12 hrs. LCMS showed that the desired product was detected. The mixture was filtered, and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether: EtOAc= 10:1 to 5:1). The desired product compound **3_P2** (0.62 g, 1.14 mmol, 74.8% yield) was obtained as yellow oil. m/z (M+1) = 542.4

Step 5: Synthesis of (S)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octane-7-carbaldehyde

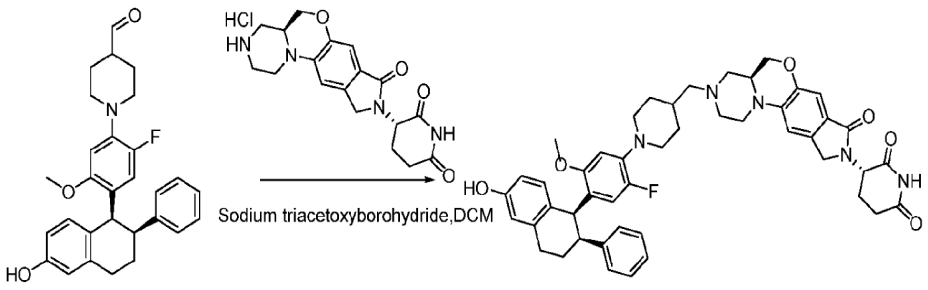
[0622] The solution of compound **3_P2** (0.1 g, 184 μmol, 1 eq) in formic acid (2 mL) was stirred for 1 hr at 20 °C. LCMS showed that compound 3_P2 was consumed, and the desired product was detected. The mixture was concentrated under reduced pressure. The desired product compound 4_P2 (0.08 g, 98.6% yield) was obtained as a yellow oil. m/z (M+1) =440.2

Step 6: Synthesis of (S)-3-(1'-(((R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

[0623] To the suspension of compound **5** (71.3 mg, 182 umol, 1 eq, HCl) in DMF (2 mL) was saturated KOAc (18.7 mg, 191 umol, 1.05 eq) at 20 °C. After 10 min, the reaction mixture was cooled to 0 °C, and NaBH(OAc)3 (57.86 mg, 273 umol, 1.5 eq) was added to the mixture. The solution of compound 4_P2 (0.08 g, 182 umol, 1 eq) in formic acid (1 mL) was added at 0 °C, and stirred for 1 hr at 0 °C. LCMS showed that compound 4_P2 was consumed and the desired product was detected. The mixture was quenched with water (0.1 mL), and purified by pre-HPLC (column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [water (FA)-ACN]; B%: 30%-60%,8min). The desired product **Compound A75**, (0.064 g, 44.7% yield, 99.2% purity) was obtained as a white solid.

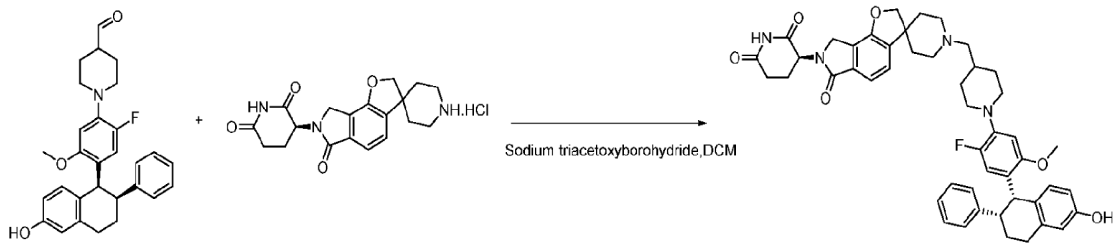
[0624] ^{1}H NMR (400MHz, DMSO-d6) δ10.98 (s, 1H), 9.10 (s, 1H), 7.40 (d, J=7.6 Hz, 1H), 7.27 (d, J=7.6 Hz, 1H), 7.20 - 7.05 (m, 3H), 6.83 (br d, J=6.8 Hz, 2H), 6.69 - 6.58 (m, 2H), 6.48 (dd, J=2.4, 8.3 Hz, 1H), 6.18 (d, J=8.5 Hz, 2H), 6.06 (d, J=8.6 Hz, 2H), 5.09 (dd, J=4.9, 13.4 Hz, 1H), 4.57 - 4.48 (m, 2H), 4.38 (d, J=17.2 Hz, 1H), 4.22 (d, J=17.2 Hz, 1H), 4.12 (br d, J=4.9 Hz, 1H), 3.87 (t, J=7.5 Hz, 1H), 3.75 (dd, J=7.7, 16.0 Hz, 2H), 3.64 (d, J=7.6 Hz, 1H), 3.58 - 3.45 (m, 2H), 3.26 (br s, 1H), 3.06 - 2.82 (m, 5H), 2.64 - 2.53 (m, 2H), 2.46 - 2.21 (m, 4H), 2.15 - 1.82 (m, 7H), 1.70 (br d, J=9.1 Hz, 3H). m/z (M+1) =779.3.

Compound A91: (S)-3-((S)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-3,4,4a,5-tetrahydro-1H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9(2H,8H,10H)-yl)piperidine-2,6-dione



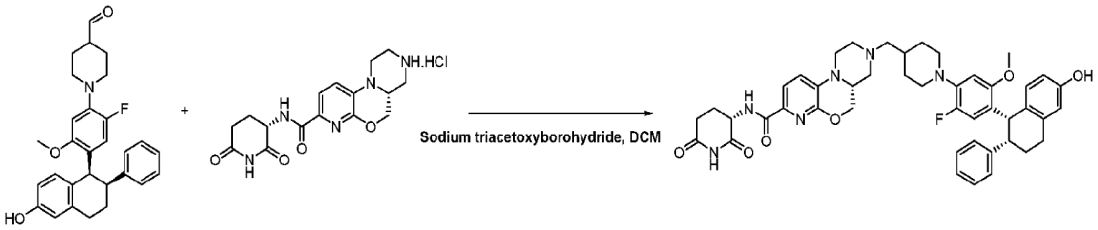
[0625] To a mixture of 1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidine-4-carbaldehyde (55 mg, 0.12 mmol 1 eq.), (S)-3-((S)-8-oxo-3,4,4a,5-tetrahydro-1H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9(2H,8H,10H)-yl)piperidine-2,6-dione hydrochloride (70 mg, 0.17 mmol 1.5 eq.) in DCM (2 mL) was added sodium triacetoxyborohydride (51 mg, 0.24 mmol 2.0 eq.) The resultant mixture was then stirred at 25°C for 2h. LCMS showed the reaction was completed. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((S)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-3,4,4a,5-tetrahydro-1H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9(2H,8H,10H)-yl)piperidine-2,6-dione (46.68 mg, 48.7 % yield) as a white solid. LC-MS (ESI, m/z): mass calcd. For $C_{47}H_{50}FN_5O_6$,799.37; found, 800.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.34 (s, 1H), 7.11 – 7.02 (m, 4H), 6.93 (s, 1H), 6.76 (d, J = 7.8 Hz, 2H), 6.60 – 6.52 (m, 2H), 6.50 – 6.43 (m, 1H), 6.22 – 6.14 (m, 2H), 5.09 – 4.98 (m, 1H), 4.67 (d, J = 5.0 Hz, 1H), 4.33 – 4.15 (m, 3H), 3.93 – 3.81 (m, 2H), 3.29 – 3.22 (m, 4H), 2.98 – 2.88 (m, 8H), 2.80 – 2.72 (m, 1H), 2.64 – 2.56 (m, 3H), 2.38 – 2.25 (m, 2H), 2.23 – 2.05 (m, 4H), 1.98 – 1.92 (m, 1H), 1.77 – 1.60 (m, 4H), 1.29 – 1.20 (m, 2H).

Compound A93: (S)-3-(1'-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0626] To a mixture of 1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidine-4-carbaldehyde(50.0 mg, 109 µmol, 1 eq.), (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione hydrochloride (61.4 mg, , 157 µmol, 1.2 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL)was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (55 mg, 0.26 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (45.13 mg, 56.49 µmol, 43.3 %) as a white solid. LC-MS purity: 98.8% (UV at 254 nm), 799.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.20 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.13 – 7.05 (m, 3H), 6.76 (d, J = 6.2 Hz, 2H), 6.62 – 6.54 (m, 2H), 6.49 – 6.44 (m, 1H), 6.23 – 6.15 (m, 2H), 5.12 – 4.98 (m, 1H), 4.67 (d, J = 5.4 Hz, 1H), 4.51 (t, J = 10.0 Hz, 2H), 4.40 – 4.33 (m, 1H), 4.26 – 4.16 (m, 1H), 3.00 – 2.81 (m, 9H), 2.68 – 2.54 (m, 3H), 2.47 – 2.31 (m, 2H), 2.24 – 2.14 (m, 3H), 2.05 – 1.88 (m, 5H), 1.82 – 1.74 (m, 2H), 1.70 – 1.54 (m, 4H), 1.31 – 1.17 (m, 2H).

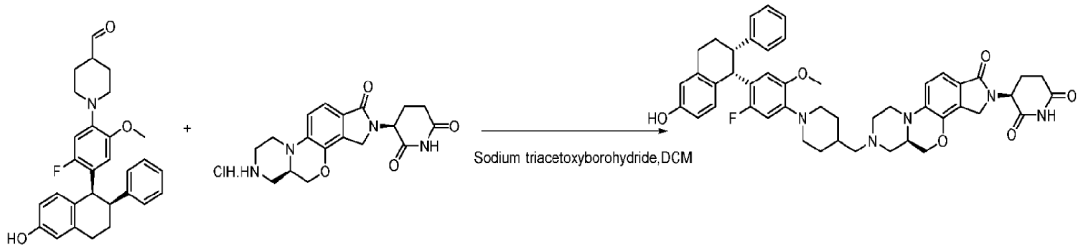
Compound A94: (R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide



[0627] To a mixture of 1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidine-4-carbaldehyde (50.0 mg, 109 µmol, 1 eq.), (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride (59.8 mg, , 153 µmol, 1.5 eq.) TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL)was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (55 mg, 0.26 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid)

to afford (R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide (63.87 mg, 80.96 µmol, 62.0 %) as a white solid. LC-MS purity: 95.5% (UV at 254 nm), 789.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.50 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 6.6 Hz, 3H), 6.76 (d, J = 6.2 Hz, 2H), 6.61 – 6.53 (m, 2H), 6.49 (d, J = 8.2 Hz, 1H), 6.25 – 6.13 (m, 2H), 4.81 – 4.63 (m, 2H), 4.44 (d, J = 8.4 Hz, 1H), 4.13 – 3.98 (m, 1H), 3.84 – 3.76 (m, 1H), 3.26 – 3.20 (m, 4H), 2.99 – 2.93 (m, 6H), 2.81 – 2.72 (m, 2H), 2.65 – 2.54 (m, 2H), 2.30 – 2.07 (m, 6H), 2.02 – 1.95 (m, 1H), 1.83 – 1.59 (m, 6H), 1.32 – 1.18 (m, 3H).

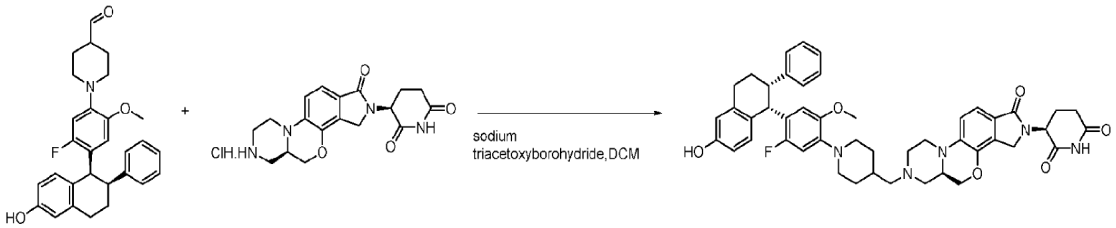
Compound A97: (S)-3-((R)-7-((1-(5-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0628] To a mixture of 1-(5-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)piperidine-4-carbaldehyde (30.0 mg, 65.3 µmol, 1 eq,), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride (49.8 mg, , 163 µmol, 1.5 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL)was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (46 mg, 0.22 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((R)-7-((1-(5-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (24.57 mg, 30.71 µmol, 47.1 %) as a white solid. LC-MS purity: 98.2% (UV at 254 nm), 800.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.14 – 7.07 (m, 3H), 7.01 (d, J = 8.6 Hz, 1H), 6.87 – 6.81 (m, 2H), 6.69 – 6.58 (m, 2H), 6.55 – 6.47 (m, 1H), 6.26 (d, J =

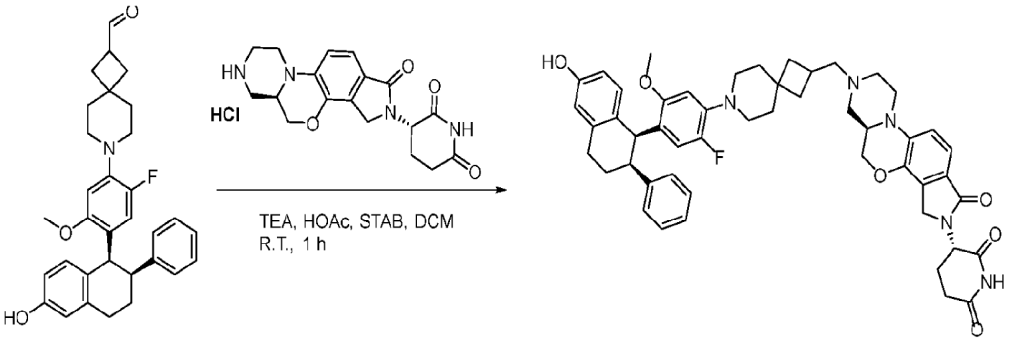
12.0 Hz, 1H), 6.06 (d, J = 7.0 Hz, 1H), 5.07 – 4.98 (m, 1H), 4.45 (d, J = 5.2 Hz, 1H), 4.40 – 4.33 (m, 1H), 4.30 – 4.22 (m, 1H), 4.14 – 4.07 (m, 1H), 4.02 – 3.94 (m, 1H), 3.86 – 3.78 (m, 1H), 3.47 (s, 3H), 3.28 – 3.16 (m, 4H), 3.04 – 2.88 (m, 5H), 2.77 – 2.65 (m, 1H), 2.62 – 2.55 (m, 1H), 2.46 – 2.28 (m, 4H), 2.27 – 2.16 (m, 3H), 2.14 – 2.05 (m, 1H), 1.98 – 1.92 (m, 1H), 1.80 – 1.69 (m, 4H), 1.65 – 1.56 (m, 1H), 1.29 – 1.14 (m, 2H)..

Compound A98: (S)-3-((R)-7-((1-(5-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0629] To a mixture of 1-(5-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)piperidine-4-carbaldehyde (30.0 mg, 65.3 µmol, 1 eq.), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride (30.8 mg, 78.3 µmol, 1.2 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((R)-7-((1-(5-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (24.03 mg, 30.04 µmol, 46.0 %) as a white solid. LC-MS purity: 97.8% (UV at 254 nm), 800.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.13 – 7.07 (m, 3H), 7.04 – 6.98 (m, 1H), 6.91 – 6.82 (m, 2H), 6.67 – 6.58 (m, 2H), 6.53 – 6.46 (m, 1H), 6.29 – 6.22 (m, 1H), 6.06 (d, J = 7.0 Hz, 1H), 5.08 – 4.98 (m, 1H), 4.45 (d, J = 5.2 Hz, 1H), 4.40 – 4.33 (m, 1H), 4.29 – 4.21 (m, 1H), 4.16 – 4.05 (m, 1H), 4.00 – 3.94 (m, 1H), 3.86 – 3.76 (m, 1H), 3.47 (s, 3H), 3.36 – 3.28 (m, 4H), 3.04 – 2.81 (m, 6H), 2.77 – 2.66 (m, 1H), 2.61 – 2.54 (m, 1H), 2.46 – 2.33 (m, 3H), 2.28 – 2.16 (m, 3H), 2.13 – 2.06 (m, 1H), 1.98 – 1.91 (m, 1H), 1.80 – 1.69 (m, 4H), 1.64 – 1.52 (m, 1H), 1.28 – 1.13 (m, 2H).

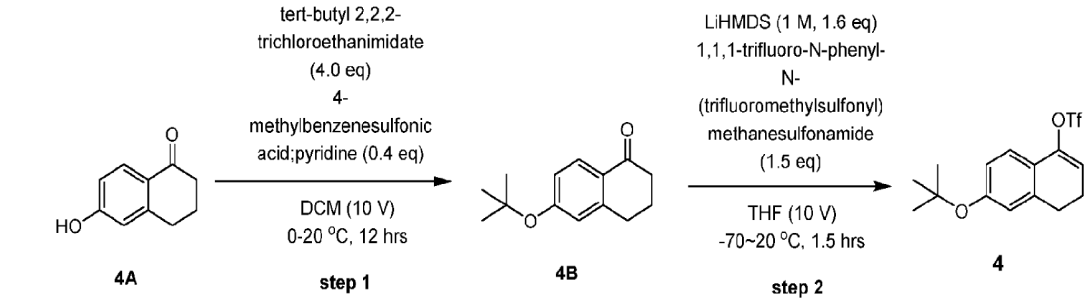
Compound A99: (S)-3-((R)-7-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

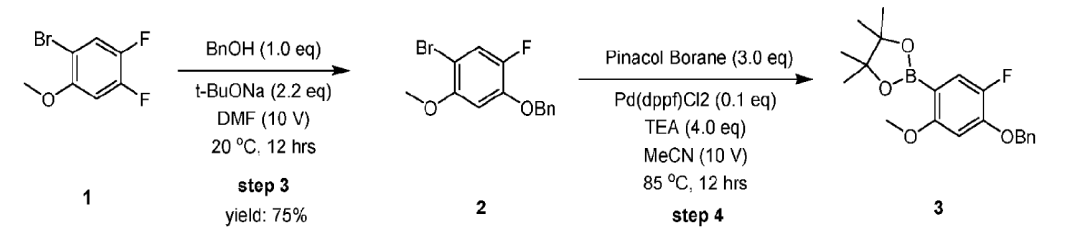


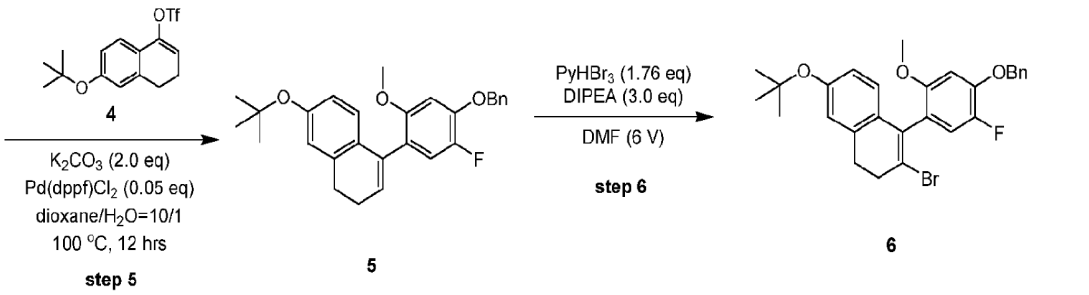
[0630] To a mixture of 7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (60 mg, 0.12 mmol, 1 eq.), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride (57 mg, 0.144 mmol, 1.2 eq.), TEA (18 mg, 0.18 mmol, 1.5 eq.) in DCM (5.0 mL) was added acetic acid (12 mg, 0.2 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (51 mg, 0.24 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-((R)-7-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (54.58 mg, 54.1% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 840.9 $[M+H]^+$

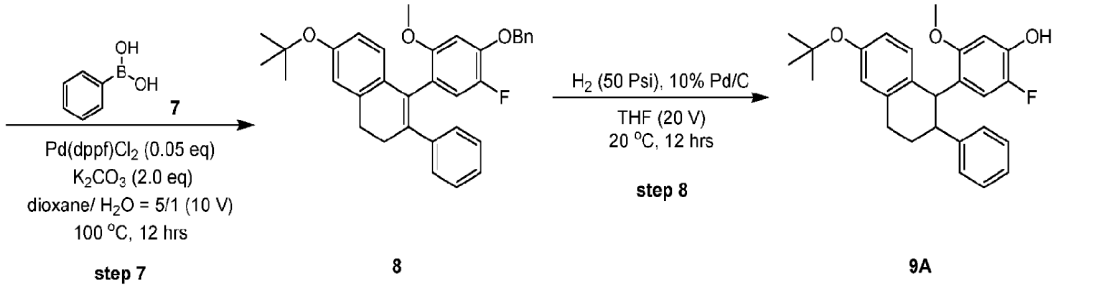
[0631] 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.21 – 6.98 (m, 5H), 6.75 (d, J = 6.4 Hz, 2H), 6.63 – 6.45 (m, 3H), 6.18 (dd, J = 10.4, 6.8 Hz, 2H), 5.03 (dd, J = 13.2, 4.8 Hz, 1H), 4.67 (d, J = 4.8 Hz, 1H), 4.30 (dd, J = 34.4, 13.6 Hz, 2H), 4.10 (d, J = 16.8 Hz, 1H), 3.95 (dd, J = 8.4, 6.8 Hz, 1H), 3.80 (d, J = 11.2 Hz, 1H), 3.25 – 3.03 (m, 4H), 2.95 (s, 3H), 2.92 – 2.69 (m, 9H), 2.57 (d, J = 16.8 Hz, 1H), 2.43 – 1.92 (m, 8H), 1.77 – 1.40 (m, 8H).

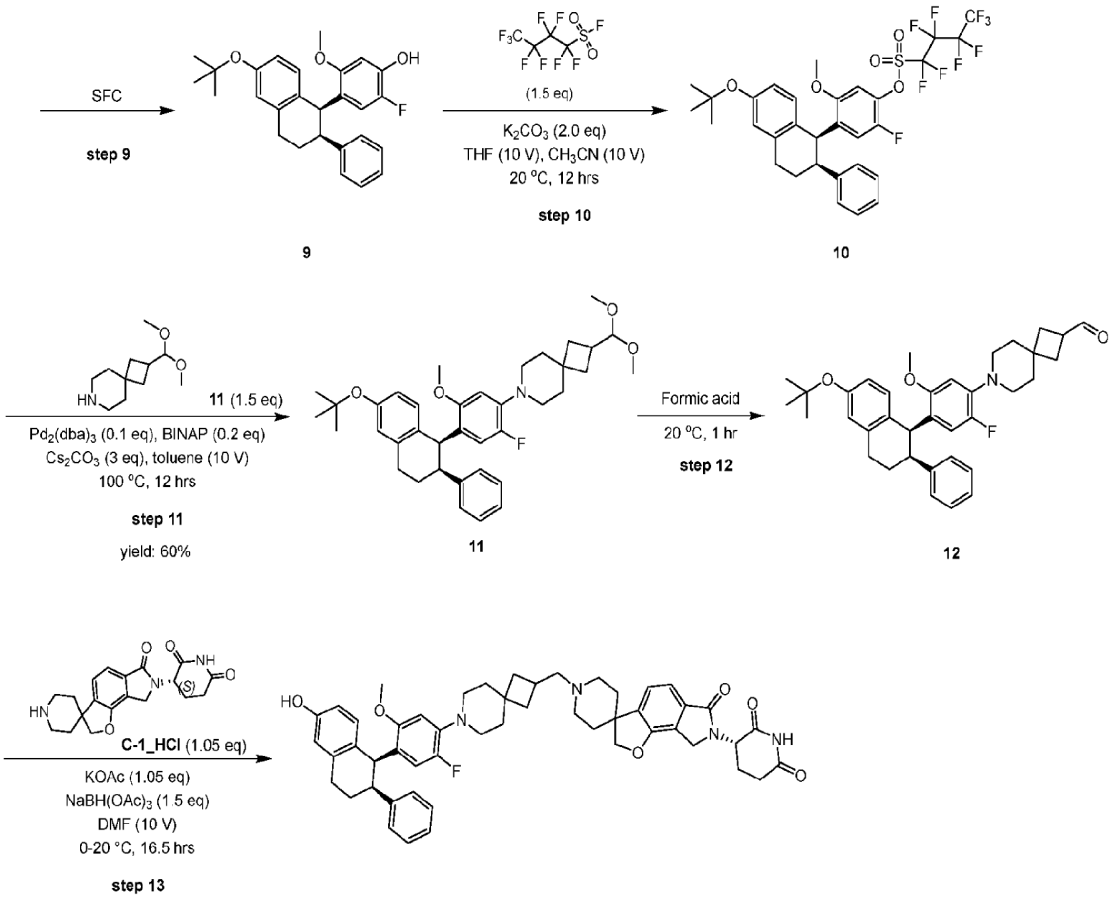
Compound A100: (S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



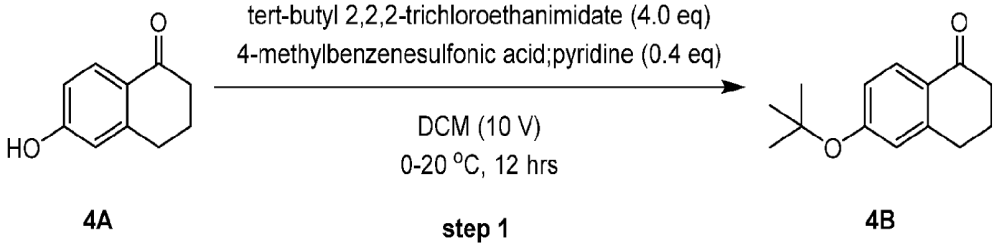








Step 1: Synthesis of 6-tert-butoxytetralin-1-one

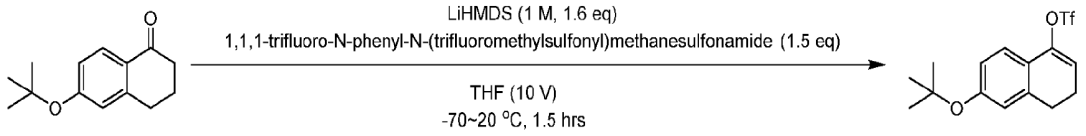


[0632] To the solution of compound **4A** (200 g, 1.23 mol, 1.00 eq) in DCM (2 L) was added 4-methylbenzenesulfonic acid; pyridine (124 g, 493 mmol, 0.40 eq) at 0 °C, before tert-butyl 2,2,2-trichloroethanimidate (1.08 kg, 4.93 mol, 883mL, 4.00 eq) was added dropwise at 0 °C under N_2 atmosphere. During which the temperature was maintained below 5 °C. The reaction mixture was warmed to 20 °C and stirred at 20 °C for 12 hrs. The mixture was filtered, and the filter cake was washed with DCM (500 mL * 2). The residue was added H_2O (500 mL) and stirred for 15 min, before the aqueous phase was extracted with DCM (500 mL * 2). The combined organic phase was washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in

vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 100/1 to 1/1). Compound **4B** (297 g, 1.27 mol, 51.3% yield, 93.0% purity) was obtained as a red oil, which was indicated by HNMR.

[0633] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 1H), 6.82 (dd, *J* = 2.0, 8.6 Hz, 1H), 6.73 (s, 1H), 2.83 (t, *J* = 6.1 Hz, 2H), 2.53 (t, *J* = 6.6 Hz, 2H), 2.04 (quin, *J* = 6.3 Hz, 2H), 1.34 (s, 9H).

Step 2: Synthesis of (6-tert-butoxy-3,4-dihydronaphthalen-1-yl) trifluoromethanesulfonate

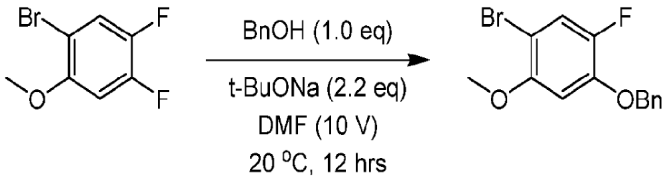


4B **step 2** **4**

[0634] To the solution of compound **4B** (100 g, 458 mmol, 1.00 eq) in THF (1 L) was added LiHMDS (1 M, 733 mL, 1.60 eq) dropwise at -70 °C under N_2 atmosphere. The reaction mixture was stirred at -70 °C for 30 min, before 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (245 g, 687 mmol, 1.50 eq) was added at -70 °C. The reaction mixture was slowly warmed to 20°C and stirred for 1 hour. The mixture was added into H_2O (500 mL) and stirred for further 15 min. The aqueous phase was extracted with EtOAc (500 mL * 2). The combined organic layer was washed with brine (500 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/EtOAc = 100/1 to 1/1). Compound **4** (136 g, 365 mmol, 79.6% yield, 94.0% purity) was obtained as a yellow solid, which was indicated by HNMR.

[0635] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 - 7.14 (m, 1H), 6.79 (dd, *J* = 2.3, 8.4 Hz, 1H), 6.74 - 6.70 (m, 1H), 5.83 (t, *J* = 4.8 Hz, 1H), 2.74 (t, *J* = 8.2 Hz, 2H), 2.41 (dt, *J* = 4.8, 8.1 Hz, 2H), 1.29 (s, 9H).

Step 1: Synthesis of 1-benzyloxy-4-bromo-2-fluoro-5-methoxy-benzene

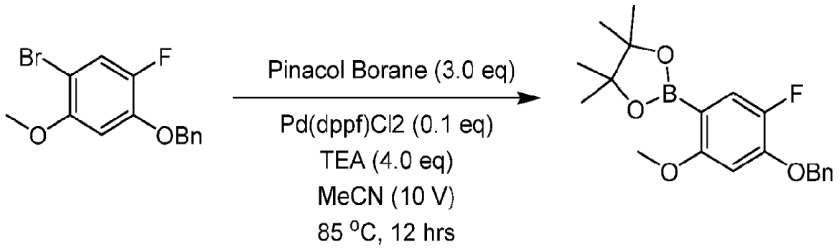


1 **step 1** yield: 75% **2**

[0636] To the solution of compound **1** (74.0 g, 332 mmol, 1.00 eq) in DMF (740 mL) was added BnOH (43.1 g, 398 mmol, 41.4 mL, 1.20 eq) dropwise at 10~20 °C. t-BuONa (70.2 g, 730 mmol, 2.20 eq) was added to the mixture in portions at 10~20 °C, and the mixture was stirred at 20 °C for 12 hrs and turned to a green solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in MTBE (1 L) and H_2O (500 mL) and extracted with MTBE (300 mL * 3). The combined organic layer was washed with brine (500 mL * 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 50/1 to 5/1). Compound **2** (100 g, 321 mmol, 96.8% yield) was obtained as an off-white solid, which was indicated by HNMR.

[0637] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 - 7.44 (m, 6 H), 6.50 (d, *J* = 7.25 Hz, 1 H), 5.06 (s, 2 H), 3.70 (s, 3 H).

Step 2: Synthesis of 2-(4-benzyloxy-5-fluoro-2-methoxy-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



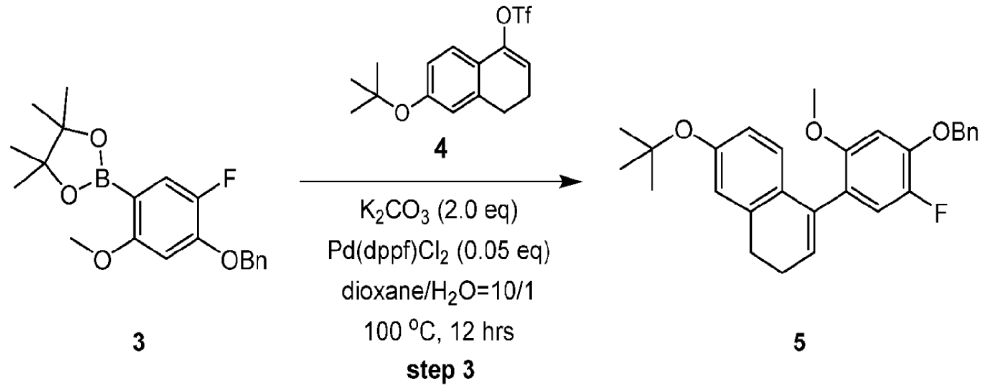
2 **step 2** **3**

[0638] The mixture of compound **2** (110 g, 353 mmol, 1.00 eq), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (136 g, 1.06 mol, 154 mL, 3.00 eq), $Pd(dppf)Cl_2$ (25.8 g, 35.4 mmol, 0.10 eq) and TEA (143 g, 1.41 mol, 197 mL, 4.00 eq) in MeCN (2.2 L) was degassed and purged with N_2 for 3 times at 20 °C, before the reaction mixture was stirred at 85 °C for 5 hrs under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was diluted with EtOAc (500 mL) and extracted with water (500 mL * 2). The combined organic layer was washed with brine (400 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 100/1 to 5/1). The residue was stirred in petroleum ether (200 mL) at 20 °C for 1 hr and precipitation was observed. The resulting suspension was filtered and concentrated under reduced pressure to give the product. Compound

3 (151 g, 379 mmol, 53.7% yield, 90.0% purity) was obtained as a white solid, which was indicated by HNMR.

[0639] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.20 (m, 6H), 6.42 (d, *J* = 6.5 Hz, 1H), 5.09 (s, 2H), 3.66 (s, 3H), 1.25 (s, 11H). m/e+1=359.

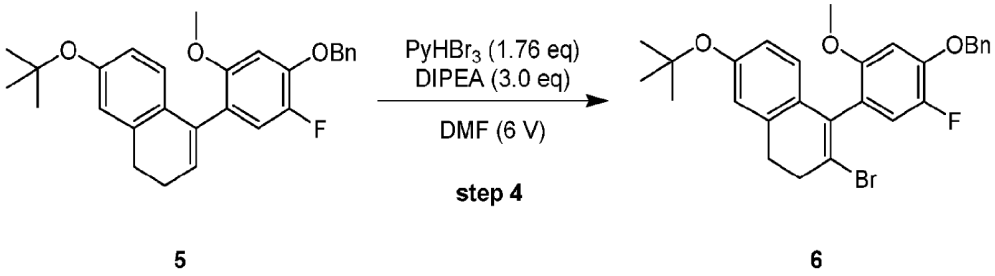
Step 3: Synthesis of 4-(4-benzyloxy-5-fluoro-2-methoxy-phenyl)-7-tert-butoxy-1,2-dihydronaphthalene



3 **5**

[0640] The mixture of compound **4** (112 g, 321 mmol, 1 eq), compound **3** (115 g, 321 mmol, 1 eq), $Pd(dppf)Cl_2$ (11.8 g, 16.0 mmol, 0.05 eq) and K_2CO_3 (68.1 g, 642 mmol, 2.00 eq) in dioxane (1120 mL) and H_2O (224 mL) was degassed and purged with N_2 for 3 times at 20 °C, before the mixture was stirred at 100 °C for 12 hrs under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 100/1 to 10/1). Compound **5** (57.0 g, 98.3 mmol, 30.6% yield, 74.6% purity) was obtained as a yellow oil. m/e+1=433.

Step 4: Synthesis of 4-(4-benzyloxy-5-fluoro-2-methoxy-phenyl)-3-bromo-7-tert-butoxy-1,2-dihydronaphthalene



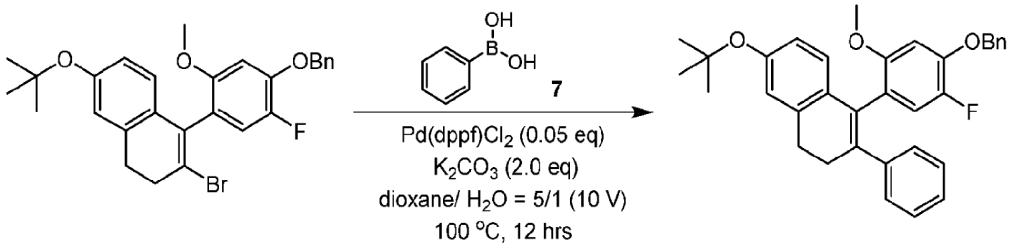
5 **6**

[0641] To the solution of compound **5** (81.0 g, 187 mmol, 1.00 eq) in DMF (486 mL) was added DIEA (72.6 g, 562 mmol, 97.9 mL, 3.00 eq) at 20 °C. $PyBr_3$ (105 g, 329 mmol, 1.76 eq) was added dropwise to the solution at 5~10 °C under N_2 atmosphere. The mixture was stirred at

5~10 °C for 18 hrs under N_2 and turned to a yellow solution. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in EtOAc (400 mL) and H_2O (200 mL), and the resulting mixture was extracted with EtOAc (200 mL * 5). The combined organic layer was washed with brine (400 mL * 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 100/1 to 10/1). Compound **6** (72.0 g, 114.04 mmol, 60.9% yield, 81.0% purity) was obtained as a yellow oil, which was detected by HNMR.

[0642] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (br d, *J* = 7.03 Hz, 2 H), 7.33 - 7.44 (m, 3 H), 6.88 (br d, *J* = 11.32 Hz, 1 H), 6.76 (br d, *J* = 1.79 Hz, 1 H), 6.60 - 6.70 (m, 2 H), 6.50 (br d, *J* = 8.46 Hz, 1 H), 5.12 - 5.28 (m, 2 H), 3.68 (s, 3 H), 2.84 - 3.09 (m, 4 H), 1.34 (s, 9 H). m/e+1=511.

Step 5: Synthesis of 4-(4-benzyloxy-5-fluoro-2-methoxy-phenyl)-7-tert-butoxy-3-phenyl-1,2-dihydronaphthalene



[0643] The mixture of compound **6** (72.0 g, 141 mmol, 1.00 eq), phenylboronic acid (18.9 g, 155 mmol, 1.10 eq), $Pd(dppf)Cl_2$ (5.15 g, 7.04 mmol, 0.05 eq) and K_2CO_3 (38.9 g, 282 mmol, 2.00 eq) in dioxane (720 mL) was degassed and purged with N_2 for 3 times at 20 °C, before the mixture was stirred at 100 °C for 12 hrs under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 100/1 to 10/1). The residue was stirred in MeOH (350 mL) at 20 °C for 3 hrs and then filtered to give the product. Compound **8** (80.0 g, crude) was obtained as a light yellow solid, which was detected by HNMR.

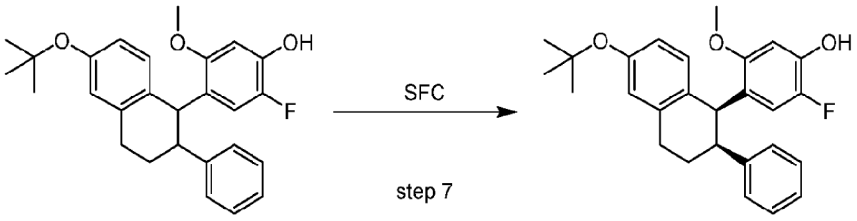
[0644] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 - 7.38 (m, 5 H), 6.91 - 7.07 (m, 5 H), 6.74 (d, *J* = 2.25 Hz, 1 H), 6.56 - 6.69 (m, 2 H), 6.48 - 6.56 (m, 1 H), 6.38 (d, *J* = 7.13 Hz, 1 H), 5.04 (s, 2 H), 3.33 (s, 3 H), 2.81 - 2.90 (m, 2 H), 2.63 - 2.78 (m, 2 H), 1.28 (s, 9 H). m/e+1=509.

Step 6: Synthesis of 4-(6-tert-butoxy-2-phenyl-tetralin-1-yl)-2-fluoro-5-methoxy-phenol

8 9A

[0645] The mixture of compound **8** (20.0 g, 39.3 mmol, 1.00 eq) and Pd/C (15.0 g, 39.3 mmol, 10% purity, 1.00 eq) in THF (420 mL) was degassed and purged with H_2 for 3 times, before the mixture was stirred at 20 °C for 12 hrs under H_2 atmosphere (50 Psi). The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was stirred in petroleum ether (200 mL) at 20 °C for 3 hrs and the mixture was filtered to give the product. Compound **9A** (15.0 g, 31.7 mmol, 80.6% yield, 88.8% purity) was obtained as a white solid.

Step 7: Synthesis of 4-[(1S,2S)-6-tert-butoxy-2-phenyl-tetralin-1-yl]-2-fluoro-5-methoxy-phenol

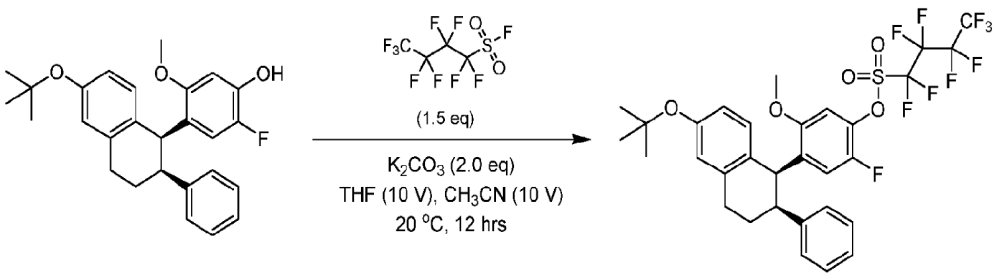


9A 9

[0646] Compound **9A** (10.0 g) was purified by chiral SFC (column: DAICEL CHIRALPAK AD (250 mm * 50 mm, 10 um); mobile phase: [0.1%NH_3H_2O IPA]; B%: 50%-50%, 6 min). Compound **9** (4.00 g, 7.1 mmol, 76.7% yield) was obtained as a yellow solid, which was indicated by HNMR.

[0647] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 - 7.09 (m, 3 H), 6.60 - 6.81 (m, 5 H), 6.26 (d, *J* = 11.76 Hz, 1 H), 6.08 (d, *J* = 7.50 Hz, 1 H), 4.94 (d, *J* = 3.88 Hz, 1 H), 4.75 (d, *J* = 5.25 Hz, 1 H), 3.24 (ddd, *J* = 13.20, 5.32, 2.13 Hz, 1 H), 2.84 - 3.03 (m, 5 H), 2.06 - 2.25 (m, 1 H), 1.64 - 1.74 (m, 1 H), 1.29 (s, 9 H).

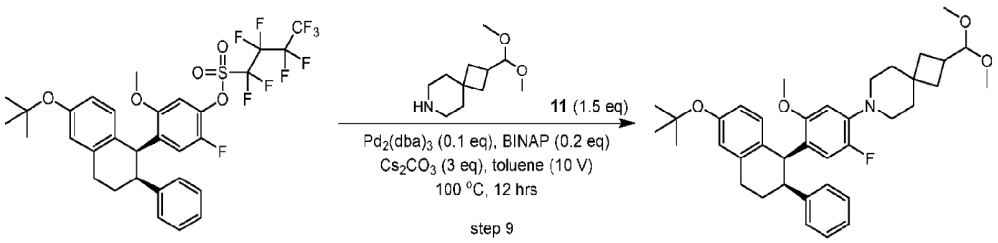
Step 8: Synthesis of [4-[(1S,2S)-6-tert-butoxy-2-phenyl-tetralin-1-yl]-2-fluoro-5-methoxy-phenyl] 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



9 10

[0648] To the solution of compound **9** (4.50 g, 10.7 mmol, 1.00 eq) in MeCN (45 mL) and THF (45 mL) was added K_2CO_3 (2.22 g, 16.05 mmol, 1.50 eq) and 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (4.85 g, 16.1 mmol, 2.82 mL, 1.50 eq) at 20 °C. The mixture was stirred at 20 °C for 12 hrs and turned to a light yellow suspension. The reaction mixture was filtered and concentrated under reduced pressure to give the crude product. Compound **10** (8.00 g, crude) was obtained as a light yellow solid.

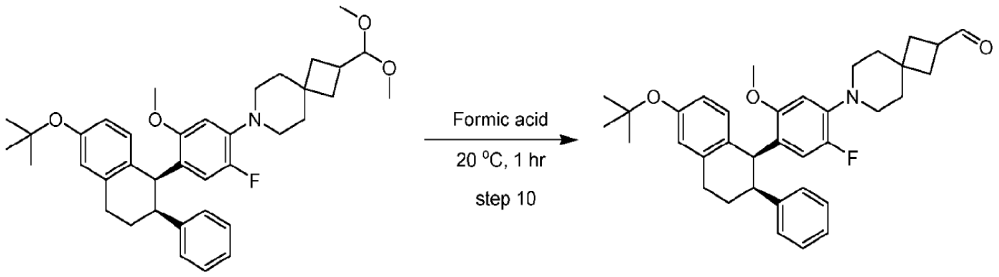
Step 9: Synthesis of 7-[4-[(1S,2S)-6-tert-butoxy-2-phenyl-tetralin-1-yl]-2-fluoro-5-methoxy-phenyl]-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane



10 11

[0649] The mixture of compound **10** (5.20 g, 7.40 mmol, 1.00 eq), compound **11** (2.21 g, 11.1 mmol, 1.50 eq), $Pd_2(dba)_3$ (678 mg, 740 umol, 0.10 eq), Cs_2CO_3 (7.23 g, 22.2 mmol, 3.00 eq) and BINAP (921 mg, 1.48 mmol, 0.20 eq) in toluene (52 mL) was degassed and purged with N_2 for 3 times at 20 °C, before the mixture was stirred at 100 °C for 12 hrs under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 50/1 to 5/1). Compound **11** (3.00 g, 4.99 mmol, 67.3% yield) was obtained as a white solid.

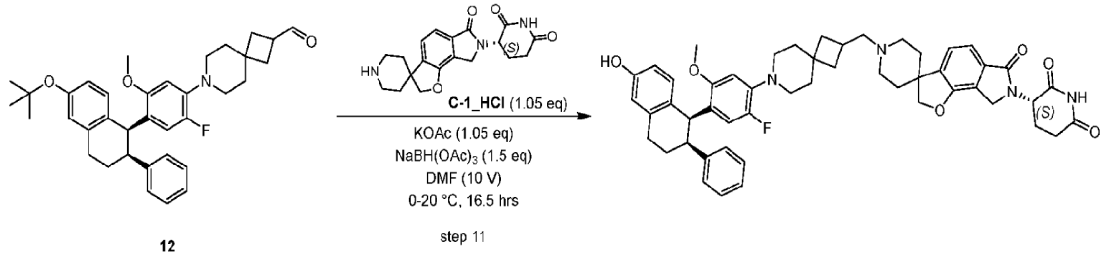
Step 10: Synthesis of 7-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-7-azaspiro[3.5]nonane-2-carbaldehyde



11 12

[0650] Compound **11** (500 mg, 831 umol, 1.00 eq) was stirred in formic acid (5 mL) at 20 °C for 1 hr, and the mixture turned to a yellow solution. The mixture was concentrated under reduced pressure to give the product (~ 2 mL solution). Compound **12** was obtained as a yellow solution.

Step 11: Synthesis of (3S)-3-[1'-[[7-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione



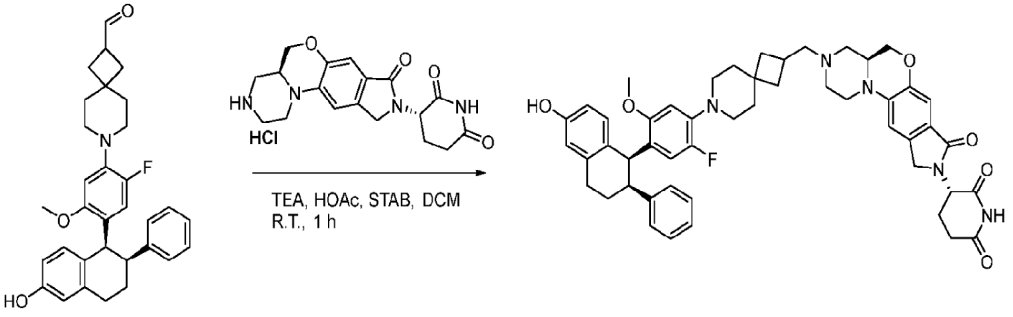
12

[0651] To the suspension of **C-1_HCl** (342 mg, 872 umol, 1.05 eq, HCl) in DMF (5 mL) was added KOAc (85.6 mg, 872.17 umol, 1.05 eq) in one portion at 20 °C, and stirred for 30 min, before being cooled to 0 °C, $NaBH(OAc)_3$ (264 mg, 1.25 mmol, 1.50 eq) and the solution of compound **12** (415 mg, 830 umol, 1.00 eq) in formic acid (2 mL) was added in portions at 0 °C. The reaction mixture was stirred at 0 °C for 4 hrs and stirred at 20 °C for 12 hrs, the mixture turned to a brown solution. The reaction mixture was poured into ice-water (100 mL) at 0 °C, before saturated $NaHCO_3$ solution was added to the mixture dropwise to adjust pH = 6. White precipitate was observed, and the mixture was filtered to give the crude product. The aqueous layer was extracted with EtOAc (50 mL * 5), and the combined organic layer was washed with brine (100 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product at 40 °C. The crude product was combined and stirred in MTBE (25 mL) for 30 minutes at 20 °C, then the mixture was filtered to give (3S)-3-[1'-[[7-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-7-azaspiro[3.5]nonan-2-yl]methyl]-6-oxo-

spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione (580 mg, 681 umol, 82.1% yield, 98.6% purity) was obtained as a white solid. LC-MS: 840.9 $[M+H]^+$.

[0652] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1 H), 9.13 (br s, 1 H), 7.22 - 7.43 (m, 2 H), 7.00 - 7.15 (m, 3 H), 6.68 - 6.81 (m, 2 H), 6.41 - 6.62 (m, 3 H), 6.11 - 6.24 (m, 2 H), 5.08 (dd, J = 13.32, 4.94 Hz, 1 H), 4.66 (br d, J = 5.00 Hz, 1 H), 4.52 (s, 2 H), 4.35 - 4.36 (m, 1 H), 4.37 (d, J = 17.13 Hz, 1 H), 4.21 (d, J = 17.13 Hz, 1 H), 3.24 (br s, 1 H), 2.72 - 2.95 (m, 12 H), 2.55 - 2.64 (m, 2 H), 2.32 - 2.46 (m, 2 H), 2.05 - 2.21 (m, 3 H), 1.83 - 2.03 (m, 6 H), 1.51 - 1.77 (m, 7 H), 1.44 (br dd, J = 9.26, 5.63 Hz, 2 H).

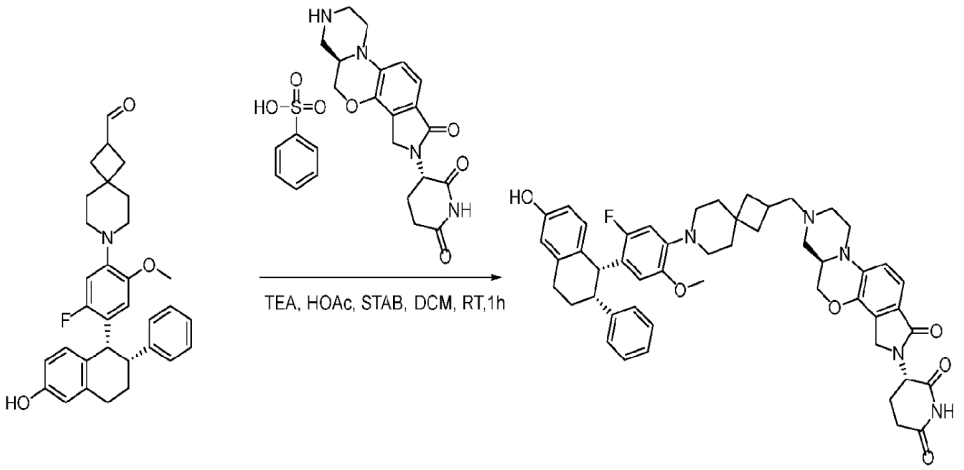
Compound A101: (S)-3-((S)-3-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0653] To a mixture of 7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (60 mg, 0.12 mmol, 1 eq.), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride (57 mg, 0.144 mmol, 1.2 eq.), TEA (18 mg, 0.18 mmol, 1.5 eq.) in DCM (5.0 mL) was added acetic acid (12 mg, 0.2 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (51 mg, 0.24 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-((S)-3-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (57.92 mg, 57.5% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 840.7 $[M+H]^+$.

[0654] ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.20 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.11 – 7.07 (m, 3H), 6.77 (d, J = 7.2 Hz, 2H), 6.59 – 6.46 (m, 3H), 6.22-6.18 (m, 2H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.67 (d, J = 5.6 Hz, 1H), 4.55-4.50 (m, 2H), 4.09-4.06 (m, 1H), 4.29(dd, J = 68.4, 17.2 Hz, 2H), 3.23-2.82 (m, 9H), 2.67-2.53 (m, 3H), 2.44 – 2.14 (m, 5H), 2.00 – 1.62 (m, 11H), 1.25 – 1.22 (m, 2H).

Compound A102: (S)-3-((R)-7-((7-(5-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

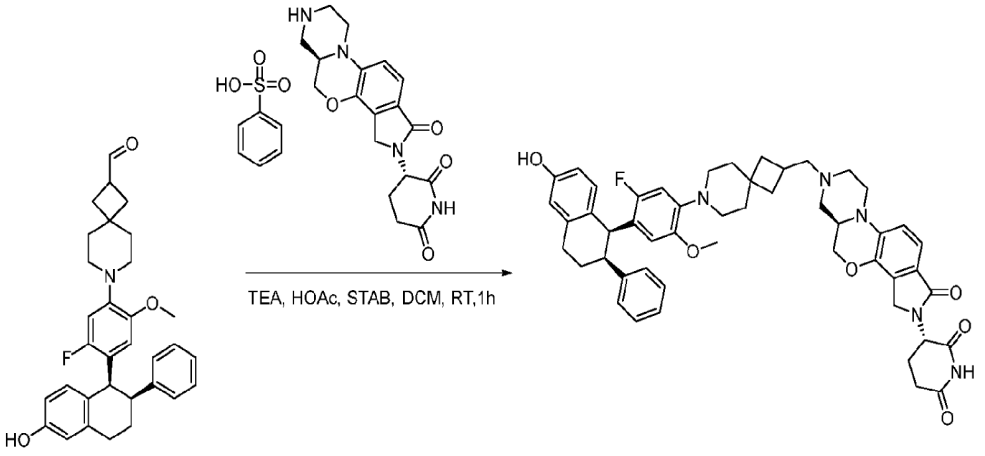


[0655] To a mixture of 7-(5-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (45.8 mg, 91.6 μmol1 eq), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione benzenesulfonic acid (61.3 mg, 119 μmol, 1.3 eq) in DCM/DMA (2 mL) was added TEA (18.5 mg, 183 μmol, 2 eq), AcOH (16.5 mg, 275 μmol, 3 eq), sodium triacetoxyborohydride (38.8 mg, 183 μmol, 3 eq) at rt. then the mixture was stirred at rt for1h. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 0% to 50% gradient in 20 min; detector, UV 214 nm to afford (S)-3-((R)-7-((7-(5-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-

1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (25 mg, yield: 32.5%) as a white solid. LC-MS purity: 100% (UV at 254 nm), 840.6 $[M+H]^+$

[0656] ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.14 (s, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.13 – 7.05 (m, 3H), 7.00 (d, J = 8.4 Hz, 1H), 6.88 – 6.78 (m, 2H), 6.68 – 6.58 (m, 2H), 6.54 – 6.45 (m, 1H), 6.24 (d, J = 11.6Hz, 1H), 6.05 (d, J = 7.2 Hz, 1H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.44 (d, J = 5.2 Hz, 1H), 4.38 – 4.31 (m, 1H), 4.26 (d, J = 16.8 Hz, 1H), 4.10 (d, J = 16.8 Hz, 1H), 4.00 – 3.90 (m, 1H), 3.80 (d, J = 11.6 Hz, 1H), 3.34 – 3.31 (m, 1H), 3.18 – 3.11 (m, 1H), 3.06 – 2.54 (m, 12H), 2.47 – 2.36 (m, 3H), 2.28 – 2.07 (m, 2H), 2.00 – 1.87 (m, 3H), 1.73 (t, J = 10.4 Hz, 2H), 1.68 – 1.60 (m, 2H), 1.57 – 1.48 (m, 2H), 1.46 – 1.35 (m, 2H).

Compound A103: (S)-3-((R)-7-((7-(5-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

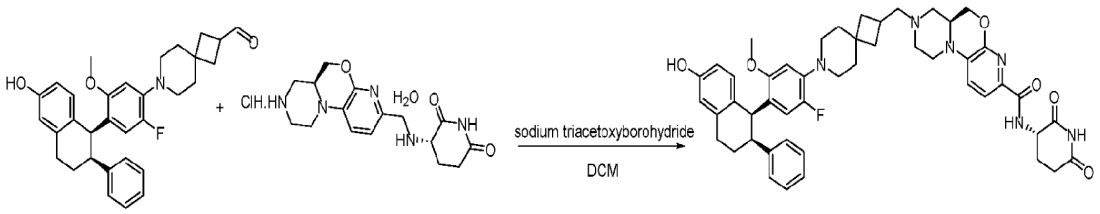


[0657] To a mixture of 7-(5-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (45.8 mg, 91.6 μmol1 eq), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione benzenesulfonic acid (61.3 mg, 119 μmol, 1.3 eq) in DCM/DMA (2 mL) was added TEA (18.5 mg, 183 μmol, 2 eq), AcOH (16.5 mg, 275 μmol, 3 eq), sodium triacetoxyborohydride (38.8 mg, 183 μmol, 3 eq) at rt. then the mixture was stirred at rt for1h. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN

in water (0.1% FA), 0% to 50% gradient in 20 min; detector, UV 214 nm to afford (S)-3-((R)-7-((7-(5-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (25 mg, yield: 32.5%) as a white solid.

[0658] LC-MS purity: 100% (UV at 254 nm), 840.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.13 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.13 – 7.05 (m, 3H), 7.00 (d, J = 8.4 Hz, 1H), 6.88 – 6.77 (m, 2H), 6.68 – 6.57 (m, 2H), 6.49 (dd, J = 8.2, 2.4 Hz, 1H), 6.24 (d, J = 11.6 Hz, 1H), 6.05 (d, J = 7.2 Hz, 1H), 5.03 (dd, J = 13.2, 4.8 Hz, 1H), 4.44 (d, J = 5.2 Hz, 1H), 4.34 (dd, J = 10.8, 2.4 Hz, 1H), 4.26 (d, J = 16.8 Hz, 1H), 4.09 (d, J = 16.8 Hz, 1H), 4.01 – 3.89 (m, 1H), 3.80 (d, J = 11.2 Hz, 1H), 3.47 (s, 3H), 3.19 – 3.10 (m, 1H), 3.08 – 2.52 (m, 12H), 2.48 – 2.30 (m, 4H), 2.30 – 2.17 (m, 1H), 2.16 – 2.05 (m, 1H), 2.01 – 1.87 (m, 3H), 1.79 – 1.69 (m, 2H), 1.68 – 1.59 (m, 2H), 1.57 – 1.47 (m, 2H), 1.45 – 1.33 (m, 2H).

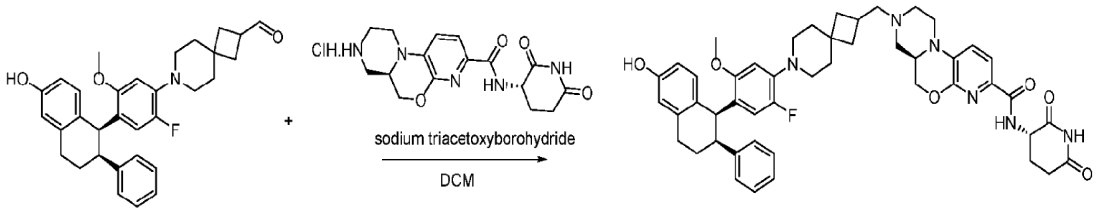
Compound A104: (S)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide



[0659] To a mixture of 7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (0.03 g, 1.0 eq, 0.06 mmol), (S)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide (0.02 g, 1.1 eq, 0.07 mmol) in DCM (3.00 mL) was added sodium triacetoxyhydroborate (0.03 g, 2.0 eq, 0.1 mmol). The resultant mixture was stirred at 25 °C for 1 h. The residue was purified by Prep-HPLC (Acetonitrile/ 0.05% Formate acid) to afford (S)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide (24.63 mg, 50 % yield) as a white solid. LC-MS purity: 97.4% (UV at 254 nm), 829.5. $[M+H]^+$.

[0660] ^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.15 (s, 1H), 8.49 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.16 – 7.00 (m, 3H), 6.75 (d, *J* = 6.0 Hz, 2H), 6.65 – 6.42 (m, 3H), 6.26 – 6.10 (m, 2H), 4.78 – 4.61 (m, 2H), 4.43 (d, *J* = 8.4 Hz, 1H), 4.13 – 4.03 (m, 1H), 3.76 (d, *J* = 11.6 Hz, 1H), 3.30 – 3.11 (m, 4H), 3.04 – 2.93 (m, 5H), 2.92 – 2.66 (m, 10H), 2.45 – 2.33 (m, 2H), 2.21 – 2.06 (m, 3H), 2.01 – 1.89 (m, 3H), 1.79 – 1.62 (m, 4H), 1.59 – 1.53 (m, 2H), 1.48 – 1.37 (m, 2H).

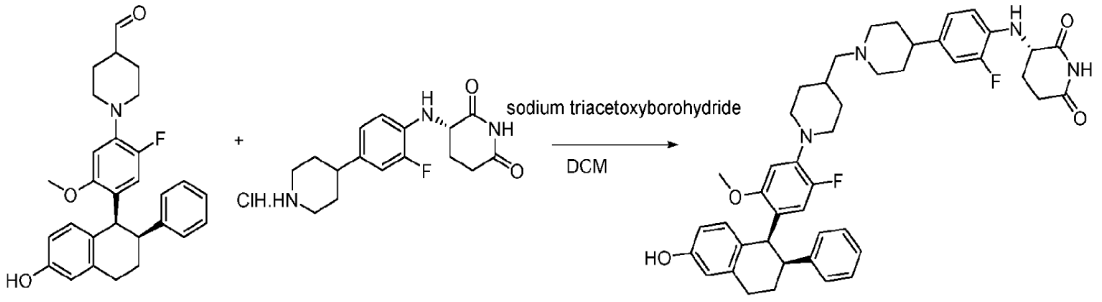
Compound A111: (R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide



[0661] To a mixture of 7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (0.06 g, 1 eq, 0.1 mmol), (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide (0.05 g, 1.1 eq, 0.1 mmol) in DCM (3.00 mL) was added sodium triacetoxyhydroborate (0.05 g, 2 eq, 0.2 mmol). The resultant mixture was then stirred at 25 °C for 1 h. The residue was purified by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide (57.52 mg, 60 % yield)as yellow solid. LC-MS purity: 95.2% (UV at 254 nm), 829.5 $[M+H]^+$.

[0662] ^{1}H NMR (400 MHz, DMSO) δ 10.82 (s, 1H), 9.11 (s, 1H), 8.48 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.08 (M, 3H), 6.75 (d, *J* = 6.8 Hz, 2H), 6.62 – 6.51 (m, 2H), 6.51 – 6.45 (m, 1H), 6.26 – 6.11 (m, 2H), 4.77 – 4.63 (m, 2H), 4.43 (d, *J* = 10.8 Hz, 1H), 4.12 – 4.01 (m, 1H), 3.76 (d, *J* = 11.6 Hz, 1H), 3.27 – 3.12 (m, 3H), 3.01 – 2.92 (m, 5H), 2.92 – 2.69 (m, 9H), 2.46 – 2.36 (m, 2H), 2.22 – 2.06 (m, 3H), 2.01 – 1.90 (m, 3H), 1.75 – 1.53 (m, 6H), 1.47 – 1.38 (m, 2H).

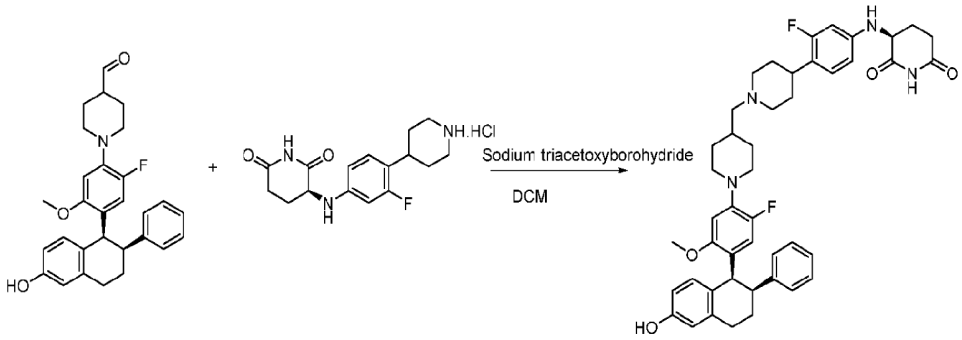
Compound A119: (S)-3-((2-fluoro-4-(1-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione



[0663] To a mixture of 1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidine-4-carbaldehyde (50.0 mg, 109 µmol, 1 eq.), (S)-3-((3-fluoro-2-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride (49.8 mg, , 163 µmol, 1.5 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL)was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (46 mg, 0.22 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((2-fluoro-4-(1-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione (30.38 mg, 40.57 µmol, 37.3 %) as a white solid. LC-MS purity: 95.7% (UV at 254 nm), 749.7 $[M+H]^+$.

[0664] ^{1}H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 8.31 (s, 1H), 7.09 (d, J = 6.8 Hz, 3H), 6.95 – 6.89 (m, 1H), 6.87 – 6.80 (m, 1H), 6.75 (t, J = 8.8 Hz, 3H), 6.60 – 6.53 (m, 2H), 6.50 – 6.45 (m, 1H), 6.24 – 6.15 (m, 2H), 5.38 (d, J = 6.7 Hz, 1H), 4.67 (d, J = 4.8 Hz, 1H), 4.41 – 4.32 (m, 1H), 3.30 – 3.22 (m, 4H), 2.98 – 2.90 (m, 6H), 2.80 – 2.72 (m, 1H), 2.64 – 2.56 (m, 2H), 2.39 – 2.33 (m, 1H), 2.21 – 2.14 (m, 3H), 2.09 – 1.92 (m, 4H), 1.82 – 1.68 (m, 4H), 1.65 – 1.55 (m, 4H), 1.30 – 1.19 (m, 2H).

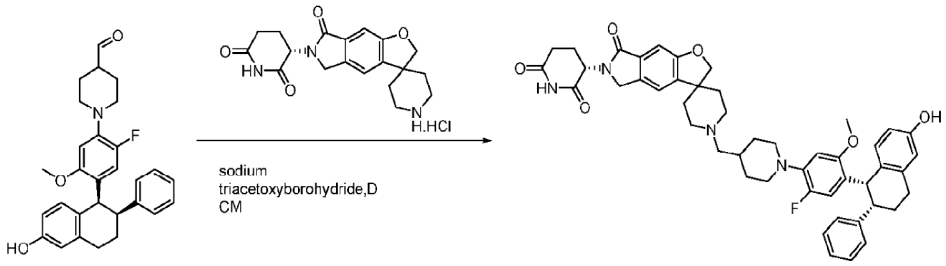
Compound A120: (S)-3-((3-fluoro-4-(1-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione



[0665] To a mixture of 1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidine-4-carbaldehyde (50.0 mg, 109 µmol, 1 eq.), (S)-3-((3-fluoro-4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride (49.8 mg, , 163 µmol, 1.5 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL)was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (46 mg, 0.22 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((3-fluoro-4-(1-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione (40.74 mg, 54.40 µmol, 50.0 %) as a white solid. LC-MS purity: 92.2% (UV at 254 nm), 749.2 $[M+H]^+$.

[0666] ^{1}H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 8.23 (s, 1H), 7.12 – 7.06 (m, 3H), 6.99 (t, J = 8.8 Hz, 1H), 6.78 – 6.73 (m, 2H), 6.60 – 6.53 (m, 2H), 6.49 – 6.39 (m, 3H), 6.22 – 6.15 (m, 2H), 5.99 (d, J = 7.6 Hz, 1H), 4.67 (d, J = 5.2 Hz, 1H), 4.34 – 4.26 (m, 1H), 3.31 – 3.22 (m, 4H), 2.97 – 2.91 (m, 6H), 2.76 – 2.69 (m, 1H), 2.64 – 2.56 (m, 3H), 2.21 – 2.14 (m, 3H), 2.12 – 2.04 (m, 1H), 2.00 – 1.85 (m, 3H), 1.81 – 1.72 (m, 2H), 1.67 – 1.56 (m, 7H), 1.29 – 1.17 (m, 2H).

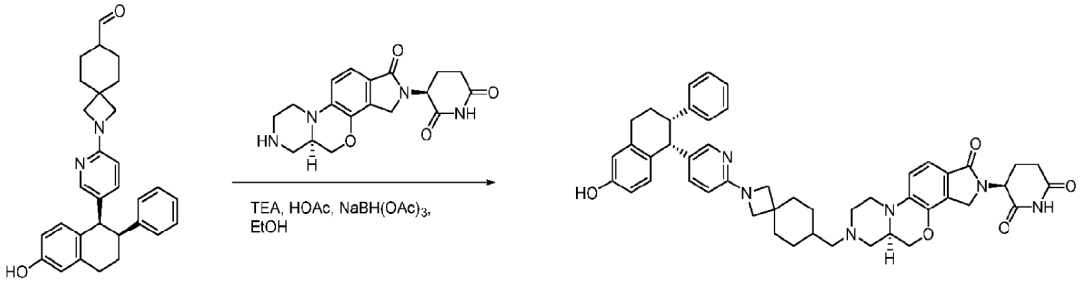
Compound A122: (S)-3-(1'-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione



[0667] To a mixture of 1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidine-4-carbaldehyde (30.0 mg, 66.1 µmol, 1 eq.), (S)-3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione hydrochloride (31.1 mg, , 79.4 µmol, 1.2 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL)was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (29.8 mg, 37.3 µmol, 57.1 %) as a white solid. LC-MS purity: 92.2% (UV at 254 nm), 799.3 $[M+H]^+$.

[0668] ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.32 (s, 1H), 7.46 (s, 1H), 7.14 – 7.06 (m, 3H), 6.99 (d, J = 9.6 Hz, 1H), 6.76 (d, J = 6.2 Hz, 2H), 6.62 – 6.53 (m, 2H), 6.50 – 6.42 (m, 1H), 6.23 – 6.15 (m, 2H), 5.12 – 5.03 (m, 1H), 4.67 (d, J = 5.2 Hz, 1H), 4.50 – 4.44 (m, 2H), 4.36 – 4.30 (m, 1H), 4.24 – 4.18 (m, 1H), 3.29 – 3.19 (m, 4H), 2.97 – 2.82 (m, 8H), 2.62 – 2.54 (m, 2H), 2.42 – 2.34 (m, 1H), 2.23 – 2.14 (m, 3H), 2.01 – 1.88 (m, 5H), 1.81 – 1.74 (m, 2H), 1.70 – 1.59 (m, 4H), 1.30 – 1.18 (m, 2H).

Compound A123: (S)-3-((R)-7-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

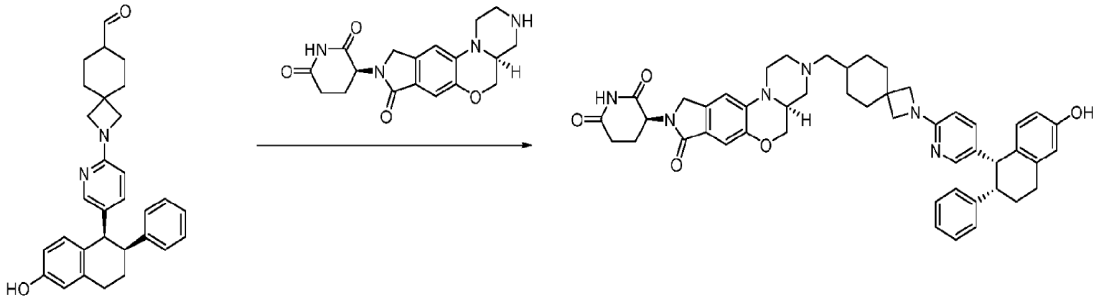


[0669] To a mixture of 2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (30 mg, 0.07 mmol, 1.2 eq.), and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in

DCM (2.0 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-((R)-7-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.8% (UV at 254 nm), 793.4 $[M+H]^+$.

[0670] ^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.13 (s, 1H), 7.25 – 7.11 (m, 4H), 7.09 – 6.85 (m, 4H), 6.75 – 6.42 (m, 4H), 6.00 (d, *J* = 8.6 Hz, 1H), 5.12 – 4.91 (m, 1H), 4.47 – 3.74 (m, 7H), 2.99 – 2.86 (m, 5H), 2.80 – 2.54 (m, 3H), 2.47 – 2.36 (m, 1H), 2.20 – 1.94 (m, 5H), 1.87 – 1.62 (m, 6H), 1.57 – 1.38 (m, 3H), 0.98 – 0.84 (m, 2H).

Compound A124: (S)-3-((S)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

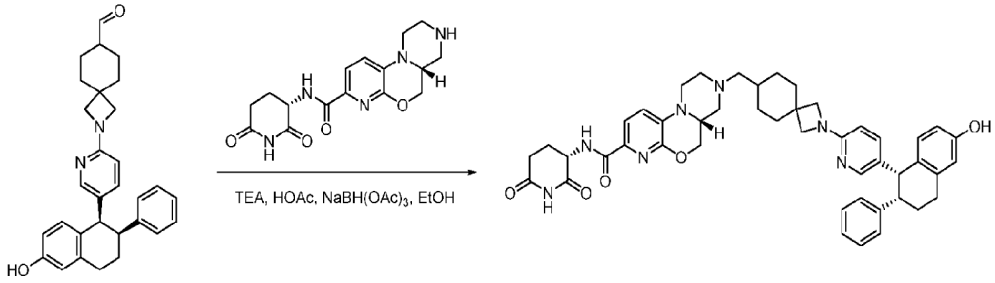


[0671] To a mixture of 2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (30 mg, 0.07 mmol, 1.2 eq.), TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford(S)-3-((S)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-

1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.8% (UV at 254 nm), 793.4 $[M+H]^+$

[0672] ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.35 (s, 1H), 7.26 – 7.08 (m, 3H), 7.06 – 6.85 (m, 5H), 6.68 – 6.48 (m, 4H), 6.00 (d, *J* = 8.6 Hz, 1H), 5.08 – 4.97 (m, 1H), 4.32 – 4.15 (m, 3H), 3.95 – 3.77 (m, 3H), 3.55 – 3.45 (m, 4H), 3.33 – 3.14 (m, 3H), 2.92 (d, *J* = 11.4 Hz, 4H), 2.16 – 1.94 (m, 6H), 1.85 – 1.66 (m, 6H), 1.42 (t, *J* = 12.4 Hz, 3H), 1.24 (s, 2H), 0.97 – 0.86 (m, 2H).

Compound A127: (R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide

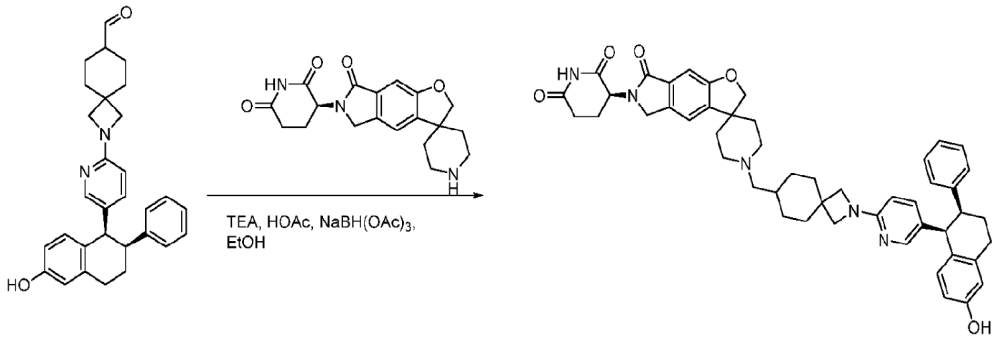


[0673] To a mixture of 2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide (30 mg, 0.07 mmol, 1.2 eq.), TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.8% (UV at 254 nm), 782.4 $[M+H]^+$.

[0674] ^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 8.31 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.22 – 7.12 (m, 3H), 7.01 (d, J = 11.8 Hz, 1H), 6.88 (d, J = 7.2 Hz, 2H), 6.70 – 6.59 (m, 2H), 6.49 (d, J = 8.2 Hz, 2H), 6.00 (d, J = 8.4 Hz, 1H), 4.78 –

4.67 (m, 1H), 4.44 (d, J = 8.6 Hz, 1H), 4.15 – 4.04 (m, 2H), 3.77 (d, J = 10.4 Hz, 1H), 3.30 (d, J = 10.8 Hz, 3H), 3.19 (s, 1H), 2.92 (d, J = 10.6 Hz, 3H), 2.75 (d, J = 8.8 Hz, 2H), 2.19 – 1.96 (m, 7H), 1.85 – 1.65 (m, 7H), 1.42 (t, J = 11.6 Hz, 4H), 1.24 (s, 1H), 0.99 – 0.86 (m, 2H).

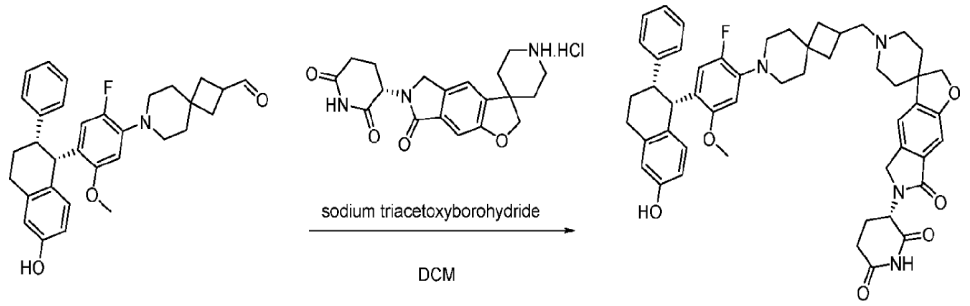
Compound A128: (S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione



[0675] To a mixture of 2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), (S)-3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (30 mg, 0.07 mmol, 1.2 eq.), TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50%Acetonitrile/ 0.05% Formic acid)) to afford (S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.8% (UV at 254 nm), 792.4 $[M+H]^+$.

[0676] ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.30 (s, 1H), 7.45 (s, 1H), 7.22 – 7.13 (m, 3H), 7.00 (s, 2H), 6.88 (d, *J* = 7.2 Hz, 2H), 6.71 – 6.56 (m, 2H), 6.50 (d, *J* = 8.4 Hz, 2H), 6.00 (d, *J* = 8.6 Hz, 1H), 5.13 – 5.04 (m, 1H), 4.45 (s, 2H), 4.39 – 4.10 (m, 4H), 3.31 (d, *J* = 13.0 Hz, 5H), 3.00 – 2.79 (m, 5H), 2.10 (d, *J* = 6.6 Hz, 2H), 2.00 – 1.79 (m, 8H), 1.67 (s, 4H), 1.49 – 1.38 (m, 3H), 1.24 (s, 2H), 0.89 (d, *J* = 12.2 Hz, 2H).

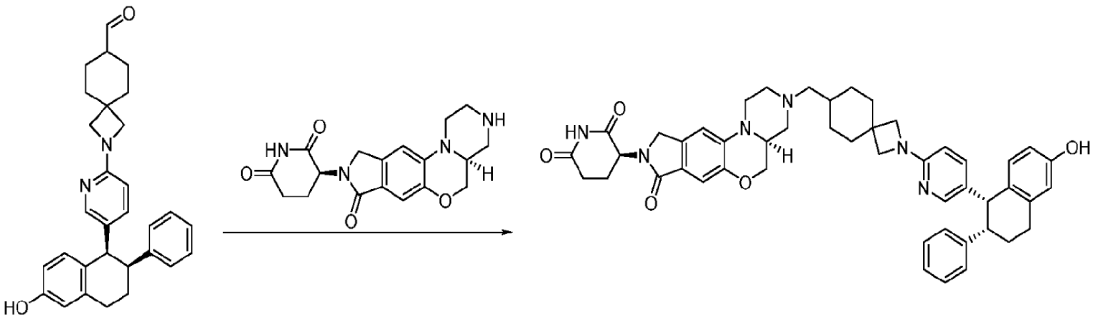
Compound A129: (S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione.



[0677] To a mixture of 7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (0.03 g, 1 eq, 0.06 mmol), (S)-3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (0.02 g, 1.1 eq, 0.07 mmol) in DCM was added sodium triacetoxyborohydride (0.03 g, 0.02 mL, 2.0 eq, 0.1 mmol). The resultant mixture was then stirred at 25 °C for 1 h. The residue was purified by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (27.75 mg, 60 % yield) as a white solid. LC-MS purity: 97.4% (UV at 254 nm), 839.4 $[M+H]^+$.

[0678] ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.30 (s, 1H), 7.44 (s, 1H), 7.12 – 6.97 (m, 4H), 6.75 (d, J = 6.4 Hz, 2H), 6.60 – 6.44 (m, 3H), 6.22 – 6.12 (m, 2H), 5.07 (dd, J = 13.2, 4.8 Hz, 1H), 4.67 (d, J = 4.8 Hz, 1H), 4.45 (s, 2H), 4.36 – 4.18 (m, 2H), 3.25 (d, J = 9.2 Hz, 1H), 2.98 – 2.75 (m, 12H), 2.64 – 2.55 (m, 1H), 2.46 – 2.29 (m, 4H), 2.19 – 2.10 (m, 1H), 2.03 – 1.85 (m, 7H), 1.70 – 1.54 (m, 7H), 1.46 – 1.38 (m, 2H)

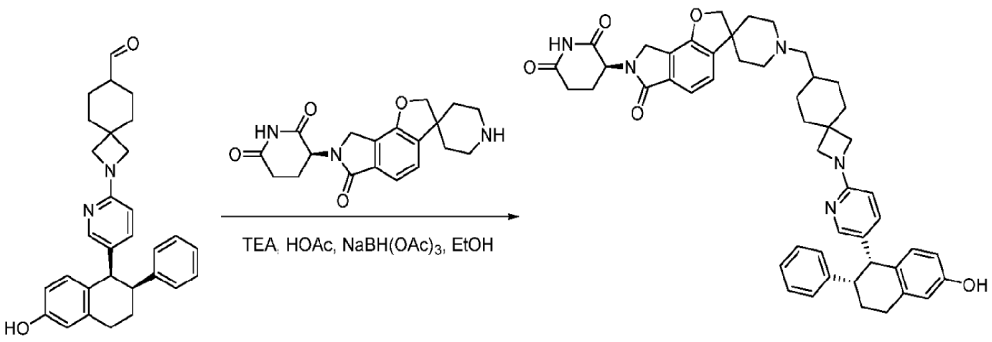
Compound A130: (S)-3-((S)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0679] To a mixture of 2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (30 mg, 0.07 mmol, 1.2 eq.), TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-((S)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.8% (UV at 254 nm), 793.4 $[M+H]^+$.

[0680] ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.41 (s, 1H), 7.23 – 7.13 (m, 3H), 7.07 – 6.83 (m, 5H), 6.70 – 6.47 (m, 4H), 6.00 (d, J = 8.6 Hz, 1H), 5.07 – 4.94 (m, 1H), 4.31 – 4.09 (m, 4H), 3.92 – 3.78 (m, 2H), 3.51 (s, 2H), 3.18 (s, 3H), 2.98 – 2.87 (m, 5H), 2.77 – 2.67 (m, 1H), 2.34 (d, J = 12.0 Hz, 1H), 2.12 – 1.95 (m, 6H), 1.74 (d, J = 11.4 Hz, 4H), 1.51 – 1.38 (m, 3H), 1.24 (s, 3H), 0.97 – 0.87 (m, 2H).

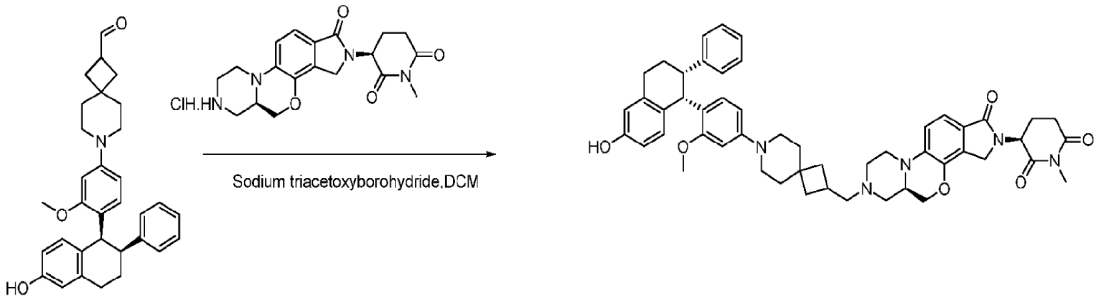
Compound A131: (S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0681] To a mixture of 2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (30 mg, 0.07 mmol, 1.2 eq.), TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.8% (UV at 254 nm), 792.4 $[M+H]^+$.

[0682] ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.31 (s, 2H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.31 – 7.12 (m, 4H), 6.99 (s, 1H), 6.88 (d, *J* = 7.4 Hz, 2H), 6.68 – 6.59 (m, 2H), 6.50 (d, *J* = 8.2 Hz, 2H), 6.00 (d, *J* = 8.4 Hz, 1H), 5.09 – 5.00 (m, 1H), 4.52 (d, *J* = 9.6 Hz, 2H), 4.37 (d, *J* = 11.2 Hz, 1H), 4.25 – 4.10 (m, 2H), 3.04 – 2.88 (m, 4H), 2.79 (d, *J* = 7.0 Hz, 3H), 2.12 – 2.00 (m, 3H), 1.98 (d, *J* = 6.8 Hz, 2H), 1.81 – 1.64 (m, 7H), 1.49 – 1.36 (m, 4H), 1.24 (s, 5H), 1.00 – 0.83 (m, 3H).

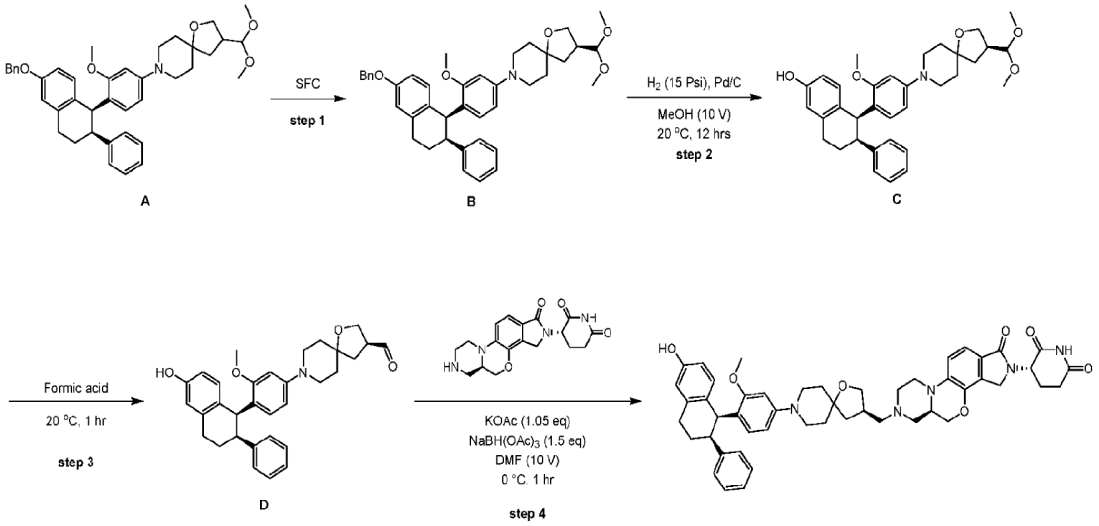
Compound A132: (S)-3-((R)-7-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)-1-methylpiperidine-2,6-dione



[0683] To a mixture of 7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (30.0 mg, 66.1 µmol, 1 eq.), (S)-1-methyl-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride (23.7 mg, , 58.1 µmol, 1.0 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL)was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((R)-7-((7-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)-1-methylpiperidine-2,6-dione (26.14 mg, 31.27 µmol, 53.8 %) as a white solid. LC-MS purity: 93.6% (UV at 254 nm), 836.8 $[M+H]^+$.

[0684] ^{1}H NMR (400 MHz, DMSO) δ 8.31 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.09 – 7.05 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.76 – 6.70 (m, 2H), 6.57 – 6.52 (m, 2H), 6.47 – 6.43 (m, 1H), 6.36 (d, J = 8.4 Hz, 1H), 6.32 – 6.27 (m, 1H), 6.10 (d, J = 1.8 Hz, 1H), 5.14 – 5.06 (m, 1H), 4.64 (d, J = 5.2 Hz, 1H), 4.37 – 4.30 (m, 1H), 4.29 – 4.21 (m, 1H), 4.15 – 4.06 (m, 1H), 4.00 – 3.93 (m, 1H), 3.83 – 3.79 (m, 1H), 3.22 – 3.14 (m, 2H), 3.02 – 2.97 (m, 6H), 2.94 – 2.88 (m, 9H), 2.77 – 2.70 (m, 2H), 2.45 – 2.37 (m, 3H), 2.18 – 2.08 (m, 2H), 1.97 – 1.91 (m, 3H), 1.79 – 1.70 (m, 1H), 1.66 – 1.57 (m, 3H), 1.54 – 1.48 (m, 2H), 1.46 – 1.38 (m, 2H).

Compound A133: (3S)-3-[(7R)-5-[[(3R)-8-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-14-oxo-9-oxa-2,5,13-triazatetracyclo[8.7.0.02,7.011,15]heptadeca-1(10),11(15),16-trien-13-yl]piperidine-2,6-dione



Step 1: Synthesis of (3S)-8-[4-[(1S,2S)-6-benzyloxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane

[0685] Compound **A** (350 mg) was purified by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [0.1% NH_3H_2O EtOH]; B%: 50%-50%, 15 min). Compound **B** (150 mg, 233 umol, 84.6% yield, 98.7% purity) was obtained as a light-yellow oil.

Step 2: Synthesis of (1S,2S)-1-[4-[(3S)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl]-2-methoxy-phenyl]-2-phenyl-tetralin-6-ol

[0686] The mixture of compound **B** (150 mg, 237 umol, 1.00 eq), Pd/C (0.10 g, 2.37 mmol, 10% purity) in MeOH (5 mL) was degassed and purged with H_2 for 3 times, and the mixture was stirred at 20 °C for 12 hrs under H_2 atmosphere (15 Psi). The reaction mixture was filtered and concentrated under reduced pressure to give the product. Compound **C** (120 mg, crude) was obtained as a colorless oil.

Step 3: Synthesis of (3S)-8-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde

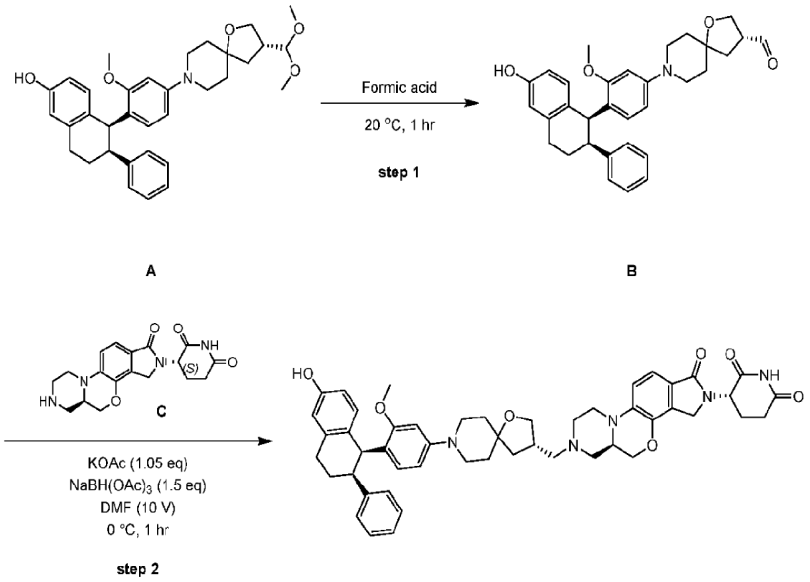
[0687] Compound **C** (60.0 mg, 110 umol, 1.00 eq) in formic acid (1 mL) was stirred at 20 °C for 1 hr and the mixture turned to a yellow solution. Acetone (1.5 mL) was added, and the reaction mixture was concentrated under reduced pressure (no water bath) to ~0.5 mL of solution. Compound **D** was obtained in a light-yellow solution and used directly in the next step. m/z (M+1): 498.

Step 4: Synthesis of (3S)-3-[(7R)-5-[[(3R)-8-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-14-oxo-9-oxa-2,5,13-triazatetracyclo[8.7.0.02,7.011,15]heptadeca-1(10),11(15),16-trien-13-yl]piperidine-2,6-dione

[0688] To the suspension of compound (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (44.8 mg, 114 umol, 1.05 eq, HCl) in DMF (1 mL) was added KOAc (11.2 mg, 114 umol, 1.05 eq) in one portion at 20 °C, and stirred for 10 minutes, before being cooled to 0 °C. $NaBH(OAc)_3$ (34.5 mg, 163 umol, 1.50 eq) and the solution of compound **D** (54.0 mg, 109 umol, 1.00 eq) in formic acid (0.5 mL) was added in one portion at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr and to a turned brown solution. The reaction mixture was quenched by the addition of H_2O (5 mL) at 0 °C, and the reaction mixture was poured into saturated $NaHCO_3$ solution (10 mL) at 0 °C. White precipitation was observed and the mixture turned to a white suspension. The mixture was filtered to give the crude product. The crude product was purified by prep-TLC (SiO_2, EtOAc: MeOH = 5:1). (3S)-3-[(7R)-5-[[(3R)-8-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-14-oxo-9-oxa-2,5,13-triazatetracyclo[8.7.0.02,7.011,15]heptadeca-1(10),11(15),16-trien-13-yl]piperidine-2,6-dione (90.4 mg, 107.9 umol, 99.4% yield, 100% purity) was obtained as a white solid.

[0689] ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1 H), 9.10 (s, 1 H), 7.01 - 7.30 (m, 5 H), 6.77 (br d, J = 6.63 Hz, 2 H), 6.57 - 6.65 (m, 2 H), 6.50 (br d, J = 7.63 Hz, 1 H), 6.31 - 6.45 (m, 2 H), 6.16 (s, 1 H), 5.08 (br dd, J = 13.45, 4.82 Hz, 1 H), 4.69 (br d, J = 4.75 Hz, 1 H), 4.41 (br d, J = 9.01 Hz, 1 H), 4.31 (br d, J = 16.76 Hz, 1 H), 4.15 (br d, J = 16.88 Hz, 1 H), 3.81 - 4.07 (m, 3 H), 3.46 - 3.53 (m, 1 H), 3.09 - 3.29 (m, 6 H), 2.87 - 3.08 (m, 8 H), 2.78 (br d, J = 9.13 Hz, 1 H), 2.58 - 2.67 (m, 2 H), 2.34 - 2.49 (m, 3 H), 2.14 - 2.28 (m, 2 H), 1.99 (br dd, J = 11.44, 7.44 Hz, 2 H), 1.56 - 1.84 (m, 6 H), 1.40 (br dd, J = 12.26, 8.38 Hz, 1 H). m/z (M+1): 838.

Compound A134: (3S)-3-[(7R)-5-[[(3S)-8-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-14-oxo-9-oxa-2,5,13-triazatetracyclo[8.7.0.02,7.011,15]heptadeca-1(10),11(15),16-trien-13-yl]piperidine-2,6-dione



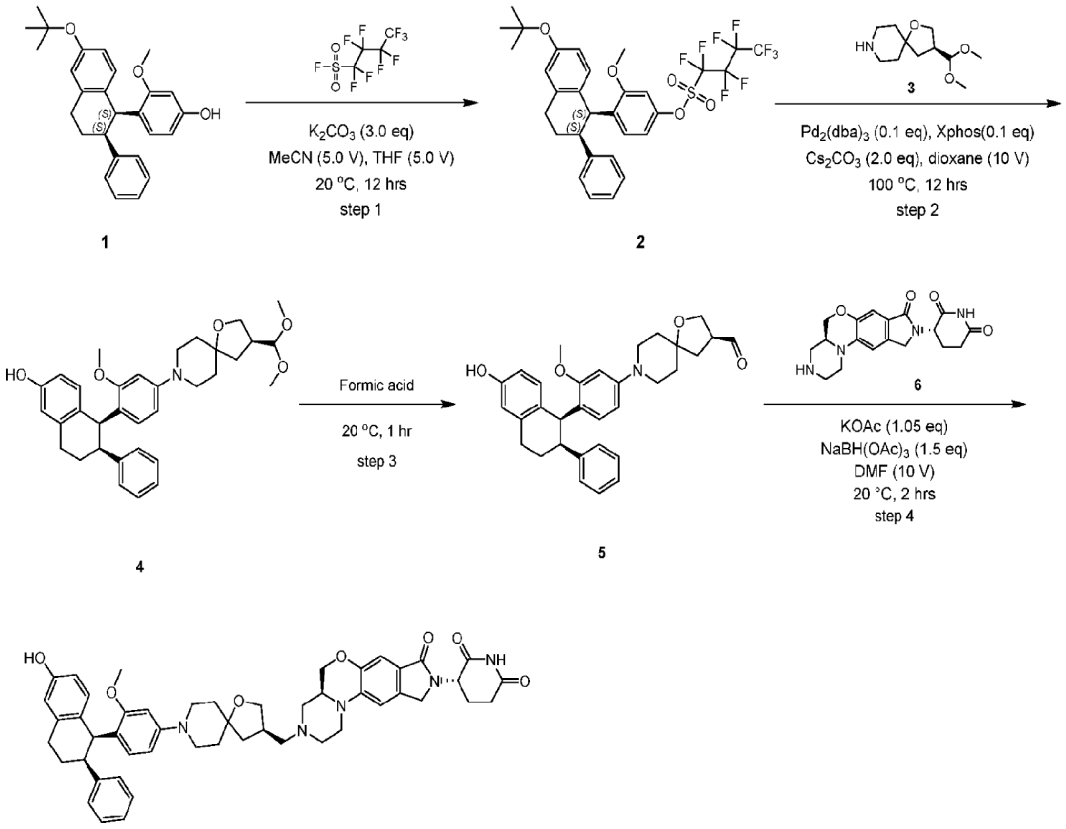
Step 1: Synthesis of (3R)-8-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde

[0690] Compound A (60.0 mg, 110 umol, 1.00 eq) in formic acid (1 mL) was stirred at 20 °C for 1 hour and the mixture turned to a yellow solution. Acetone (1.5 mL) was added, and the reaction mixture was concentrated under reduced pressure (no water bath) to ~0.5 mL of solution. Compound B was obtained in a light-yellow solution and used directly in the next step.

Step 2: Synthesis of (3S)-3-[(7R)-5-[[(3S)-8-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-14-oxo-9-oxa-2,5,13-triazatetracyclo[8.7.0.02,7.011,15]heptadeca-1(10),11(15),16-trien-13-yl]piperidine-2,6-dione

[0691] To the suspension of Compound HCl of **C** (44.7 mg, 114 µmol, 1.05 eq, HCl) in DMF (1 mL) was added KOAc (11.2 mg, 114 µmol, 1.05 eq) in one portion at 20 °C, and stirred for 10 min, before being cooled to 0 °C. $NaBH(OAc)_3$ (34.5 mg, 163 µmol, 1.50 eq) and the solution of compound B (54.0 mg, 109 umol, 1.00 eq) in formic acid (0.5 mL) was added in one portion at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr and turned to a brown solution. The reaction mixture was quenched by the addition of H_2O (5 mL) at 0 °C, and the reaction mixture was poured into saturated $NaHCO_3$ solution (10 mL) at 0 °C. White precipitate was observed and the mixture turned white suspension. The mixture was filtered to give the crude product. The residue was purified by prep-TLC (SiO_2, EtOAc: MeCN = 5:1). Compound PVT-0004711 (14.8 mg, 15.2% yield, 93.5% purity) was obtained as a white solid. m/z (M+1): 838.

Compound A135: (S)-3-((S)-3-(((R)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



Step 1: Synthesis of 4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate

[0692] To a mixture of THF (15 mL) and MeCN (15 mL) was add compound **1** (1.55 g, 11.18 mmol, 3 eq) at 20 °C, then 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (3.38 g, 11.18 mmol, 1.96 mL, 3 eq) was add to the mixture. The mixture was stirred at 20 °C for 12 hrs. TLC showed that compound **1** was consumed and the desired product was detected. The mixture was filtered, and the organic layers were concentrated under reduced pressure to give a residue. The desired product compound **2** (2.5 g, 3.65 mmol, 97.99% yield) was obtained as a white solid.

Step 2: Synthesis of (5S,6S)-5-(4-((S)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)-2-methoxyphenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

[0693] Compound **2** (2.0 g, 2.92 mmol, 1 eq) was added to dioxane (20 mL) at 20 °C; then compound **3** (943.41 mg, 4.38 mmol, 1.5 eq), $Pd_2(dba)_3$ (267.52 mg, 292.14 umol, 0.1 eq), XPhos

(139.27 mg, 292.14 umol, 0.1 eq) and Cs_2CO_3 (1.90 g, 5.84 mmol, 2 eq) were added to the mixture. The mixture was stirred at 100 °C for 12 hrs. TLC showed that a little of compound **2** was remained and the desired product was detected. The mixture was filtered, and the organic layers were concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=50:1 to 5:1). The desired product compound **4** (1.4 g, 2.33 mmol, 79.90% yield) was obtained as a yellow solid.

Step 3: Synthesis of (S)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde

[0694] A solution of compound **4** (0.7 g, 1.17 mmol, 1 eq) in formic acid (20 mL) was stirred at 20 °C for 1 hr. LCMS showed that compound **4** was consumed and the desired product was detected. The mixture was concentrated under reduced pressure to give a residue. The desired product compound **5** (0.58 g, crude) was obtained as yellow oil. m/z (M+1):498.2

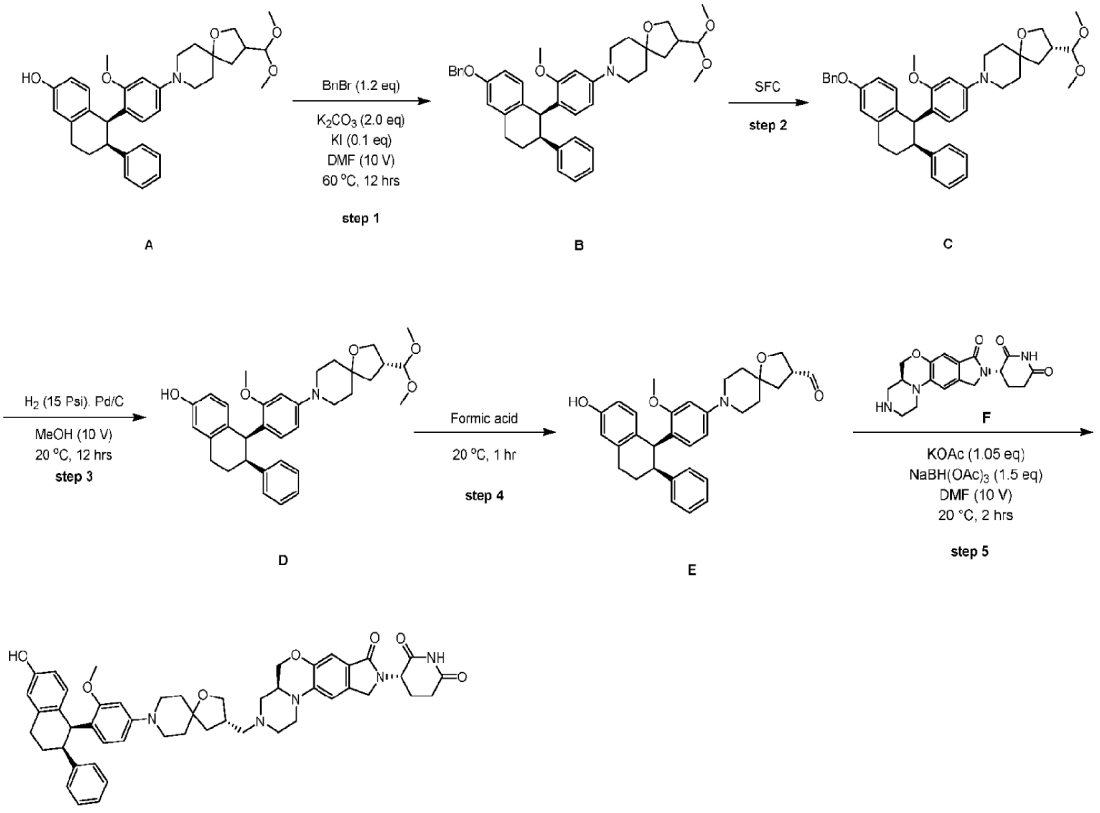
Step 4: Synthesis of (S)-3-((S)-3-(((R)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

[0695] To a solution of compound **6** (457 mg, 1.17 mmol, 1 eq, HCl) in DMF (2 mL) at 20 °C was add KOAc (120 mg, 1.22 mmol, 1.05 eq). The mixture was cooled to 0 °C and then $NaBH(OAc)_3$ (370.54 mg, 1.75 mmol, 1.5 eq) was added to the mixture. Then a solution of compound **5** (0.58 g, 1.17 mmol, 1 eq) in formic acid (0.6 mL) was added to the mixture at 0 °C. The mixture was stirred at 0 °C for 5 hrs. LCMS showed that compound **5** was consumed and the desired product was detected. The mixture was quenched with water (0.2 mL). To the product was added aq.$NaHCO_3$ and pH was adjusted to 7. The product was extracted with EtOAc (100 mL x3). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was washed with MTBE/MeCN= 10:1 (30 mL). The product was filtered, and the cake was concentrated under reduced pressure. (S)-3-((S)-3-(((R)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (0.63 g, 751 umol, 64.5% yield) was obtained as a white solid.

[0696] ^{1}H NMR (400MHz, DMSO-d6) 10.94 (s, 1H), 9.06 (s, 1H), 7.11 - 7.02 (m, 4H), 6.94 (s, 1H), 6.73 (br d, J=6.3 Hz, 2H), 6.60 - 6.53 (m, 2H), 6.46 (br d, J=8.3 Hz, 1H), 6.40 - 6.28 (m, 2H),

6.12 (s, 1H), 5.03 (br dd, J=4.8, 13.2 Hz, 1H), 4.65 (br d, J=4.9 Hz, 1H), 4.33 - 4.21 (m, 2H), 4.19 - 4.10 (m, 1H), 3.95 - 3.78 (m, 3H), 3.45 (br t, J=7.9 Hz, 1H), 3.24 - 3.16 (m, 2H), 3.12 - 3.00 (m, 5H), 2.99 - 2.88 (m, 7H), 2.82 - 2.74 (m, 1H), 2.58 (br d, J=14.8 Hz, 2H), 2.42 - 2.28 (m, 3H), 2.18 (br dd, J=6.5, 11.3 Hz, 1H), 2.12 - 2.03 (m, 1H), 2.01 - 1.90 (m, 2H), 1.75 (br t, J=10.9 Hz, 1H), 1.63 (br dd, J=5.0, 13.4 Hz, 5H), 1.35 (br dd, J=8.0, 12.5 Hz, 1H). m/z (M+1): 838.4

Compound A136: (3S)-3-[(7S)-5-[[(3S)-8-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-13-oxo-9-oxa-2,5,14-triazatetracyclo[8.7.0.02,7.012,16]heptadeca-1(17),10,12(16)-trien-14-yl]piperidine-2,6-dione



Step 1: Synthesis of 8-[4-[(1S,2S)-6-benzyloxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane

[0697] To a solution of compound **A** (370 mg, 681 µmol, 1.00 eq) in DMF (3.7 mL) was added K_2CO_3 (188 mg, 1.36 mmol, 2.00 eq), benzyl bromide (145 mg, 851 µmol, 101 uL, 1.25 eq) and KI (11.3 mg, 68.1 µmol, 0.10 eq) at 20 °C. The mixture was stirred at 60 °C for 12 hours and turned yellow suspension. The reaction mixture was quenched by addition H_2O 2 mL at 20 °C,

and then diluted with EtOAc 5 mL and extracted with EtOAc (5 mL * 4). The combined organic layers were washed with brine (10 mL * 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether: Ethyl acetate = 1:1). Compound **B** (350 mg, 552 μmol, 81.1% yield) was obtained as a yellow oil.

Step 2: Synthesis of (3R)-8-[4-[(1S,2S)-6-benzyloxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane

[0698] Compound **B** (350 mg) was purified by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [0.1% NH_3H_2O ETOH]; B%: 50%-50%, 15 min). Compound **C** (150 mg, 236 umol, 84.6% yield, 98.7% purity) was obtained as a light-yellow oil.

Step 3: Synthesis of (1S,2S)-1-[4-[(3R)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl]-2-methoxy-phenyl]-2-phenyl-tetralin-6-ol

[0699] A mixture of compound **C** (150 mg, 237 μmol, 1.00 *eq*), Pd/C (0.10 g, 2.37 mmol, 10% purity) in MeOH (1 mL) was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 20 °C for 12 hours under H_2 atmosphere (15 Psi). The reaction mixture was filtered and concentrated under reduced pressure to give the product. Compound **D** (120 mg, crude) was obtained as a colorless oil.

Step 4: Synthesis of (3R)-8-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde

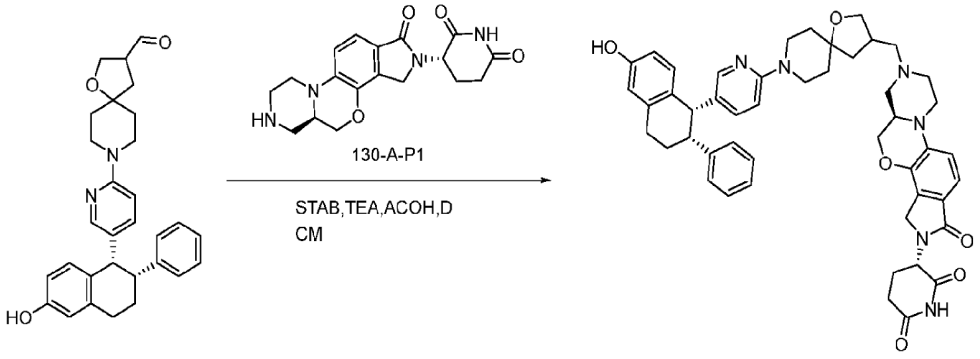
[0700] Compound **D** (40.0 mg, 73.6 umol, 1.00 eq) in formic acid (1 mL) was stirred at 20 °C for 1 hour and turned yellow solution. Acetone (1.5 mL) was added, and the reaction mixture was concentrated under reduced pressure (no water bath) to ~0.5 mL of solution. Compound **E** was obtained in a light-yellow solution and used directly in the next step. m/z (M+1):498.

Step 5: Synthesis of (3S)-3-[(7S)-5-[[(3S)-8-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-13-oxo-9-oxa-2,5,14-triazatetracyclo[8.7.0.02,7.012,16]heptadeca-1(17),10,12(16)-trien-14-yl]piperidine-2,6-dione

[0701] To the suspension of compound **F** (29.8 mg, 75.9 μmol, 1.05 eq, HCl) in DMF (1 mL) was added KOAc (7.45 mg, 75.9 μmol, 1.05 eq) in one portion at 20 °C, and stirred for 10 minutes, before cooled to 0 °C, $NaBH(OAc)_3$ (23.0 mg, 109 μmol, 1.50 eq) and the solution of compound **E** (36.0 mg, 72.3 μmol, 1.00 eq) in formic acid (0.5 mL) was added in one portion at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour and turned brown solution. The reaction mixture was quenched by addition H_2O 5 mL at 0 °C, and then the reaction mixture was poured into

saturated $NaHCO_3$ solution (10 mL) at 0 °C. White solid formed and the mixture turned white suspension. The mixture was filtered to give the crude product. The crude product was purified by prep-TLC (SiO_2, EtOAc: MeOH = 5:1). (3S)-3-[(7S)-5-[[(3S)-8-[4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-3-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-13-oxo-9-oxa-2,5,14-triazatetracyclo[8.7.0.02,7.012,16]heptadeca-1(17),10,12(16)-trien-14-yl]piperidine-2,6-dione (33.4 mg, 39.8 µmol, 55.0% yield, 100% purity) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1 H), 9.06 (s, 1 H), 6.88 - 7.14 (m, 5 H), 6.72 (br d, *J* = 6.25 Hz, 2 H), 6.51 - 6.62 (m, 2 H), 6.45 (dd, *J* = 8.25, 1.88 Hz, 1 H), 6.24 - 6.39 (m, 2 H), 6.11 (s, 1 H), 5.02 (br dd, *J* = 13.13, 5.00 Hz, 1 H), 4.64 (br d, *J* = 4.88 Hz, 1 H), 4.07 - 4.33 (m, 3 H), 3.73 - 3.96 (m, 3 H), 3.43 - 3.47 (m, 1 H), 3.04 - 3.25 (m, 7 H), 2.87 - 3.01 (m, 7 H), 2.76 (br t, *J* = 10.69 Hz, 1 H), 2.53 - 2.63 (m, 2 H), 2.26 - 2.42 (m, 3 H), 2.10 - 2.25 (m, 2 H), 1.86 - 2.00 (m, 2 H), 1.53 - 1.72 (m, 6 H), 1.34 (br dd, *J* = 12.63, 8.38 Hz, 1 H). m/z (M+1):838.

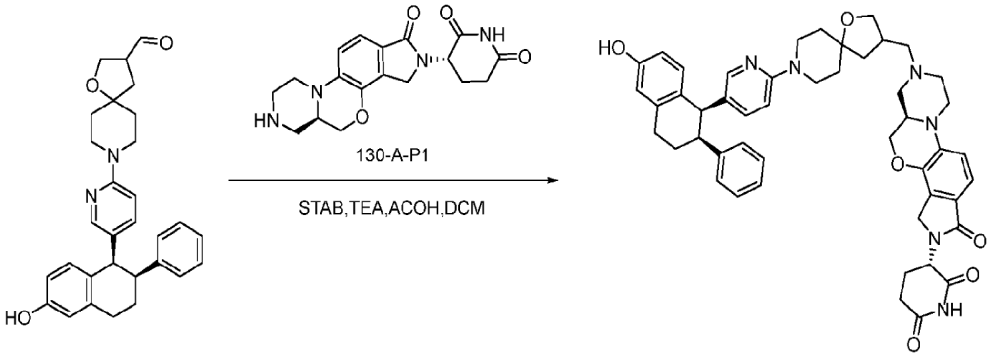
Compound A137: (3S)-3-((5aR)-7-((8-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0702] To a mixture of 8-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (30 m g, 0.064 mmol 1 eq.), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (25.1 mg, 0.071 mmol 1.1eq.) TEA (9.7 mg, 0.096 mmol, 1.5 eq.) in DCM (2 mL),) was added acetic acid (6.5 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (26.2 mg, 0.12 mmol 2.0 eq.) The resultant mixture was then stirred at 25°C for 2h. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified

by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (3S)-3-((5aR)-7-((8-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (23.9 mg, 46.1 % yield) as a white solid. LC-MS (ESI, m/z): mass calcd. For $C_{50}H_{55}N_5O_6$, 821.42; found, 822.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.31 (s, 1H), 7.22 – 7.10 (m, 4H), 7.05 – 6.97 (m, 2H), 6.88 (d, *J* = 7.2 Hz, 2H), 6.69 – 6.56 (m, 2H), 6.54 – 6.44 (m, 3H), 5.07 – 4.98 (m, 1H), 4.35 (d, *J* = 9.8 Hz, 1H), 4.30 – 4.20 (m, 1H), 4.13 – 4.05 (m, 2H), 4.00 – 3.77 (m, 3H), 3.53 – 3.39 (m, 4H), 3.22 – 3.06 (m, 2H), 3.04 – 2.84 (m, 5H), 2.77 – 2.66 (m, 1H), 2.63 – 2.52 (m, 2H), 2.45 – 2.25 (m, 4H), 2.15 – 1.90 (m, 4H), 1.81 – 1.62 (m, 2H), 1.59 – 1.39 (m, 4H), 1.38 – 1.24 (m, 1H).

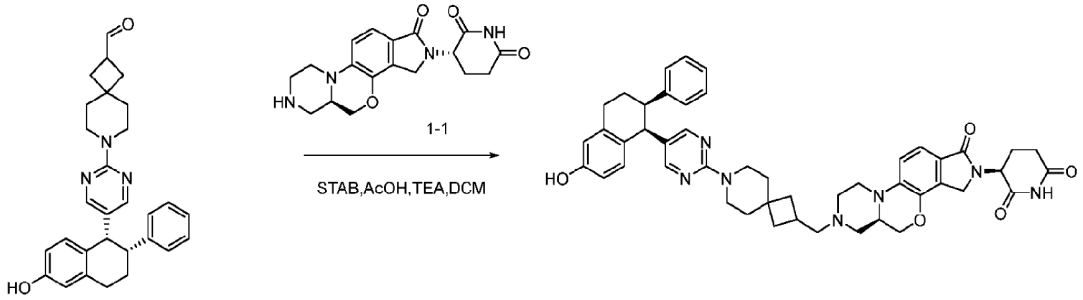
Compound A138: (3S)-3-((5aR)-7-((8-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0703] To a mixture of 8-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (30 m g, 0.064 mmol 1 eq.), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (25.1 mg, 0.071 mmol 1.1eq.) TEA (9.7 mg, 0.096 mmol, 1.5 eq.) in DCM (2 mL) was added acetic acid (6.5 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (26.2 mg, 0.12 mmol 2.0 eq.) The resultant mixture was then stirred at 25°C for 2h. The reaction was cooled to 20 °C. The residue was purified by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (3S)-3-((5aR)-7-((8-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-

1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (14.78 mg, 28.7 % yield) as a white solid. LC-MS (ESI, m/z): mass calcd. For $C_{50}H_{55}N_5O_6$, 821.42; found, 822.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.43 (s, 1H), 7.22 – 7.09 (m, 4H), 7.07 – 6.98 (m, 2H), 6.88 (d, J = 6.6 Hz, 2H), 6.67 (d, J = 8.6 Hz, 1H), 6.60 (s, 1H), 6.54 – 6.44 (m, 3H), 5.07 – 4.98 (m, 1H), 4.39 – 4.20 (m, 2H), 4.16 – 4.04 (m, 2H), 4.00 – 3.77 (m, 3H), 3.50 – 3.41 (m, 4H), 3.21 – 3.05 (m, 2H), 3.03 – 2.83 (m, 5H), 2.79 – 2.54 (m, 2H), 2.41 – 2.31 (m, 4H), 2.16 – 1.86 (m, 5H), 1.82 – 1.60 (m, 3H), 1.56 – 1.42 (m, 4H), 1.35 – 1.20 (m, 2H).

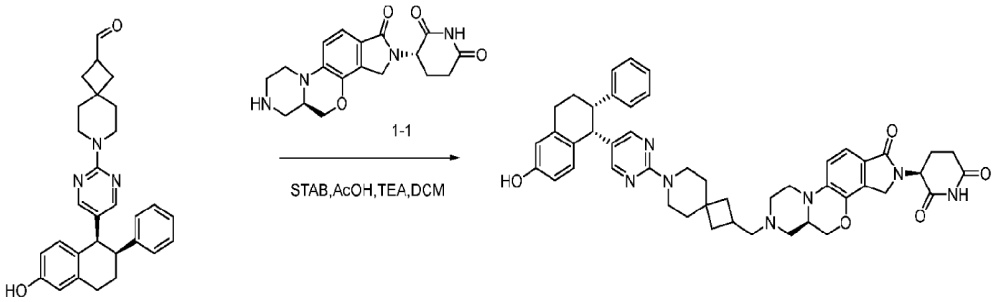
Compound A139: (S)-3-((R)-7-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0704] To a mixture of 7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonane-2-carbaldehyde (25.0 mg, 1 Eq, 55.1 µmol), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (23.6 mg, 1.2 Eq, 66.1 µmol), TEA (10.6 mg, 0.13 mmol, 1.5 eq.) in DCM (8.0 mL) was added acetic acid (7.6 mg, 0.11 mmol, 1.8 eq.) followed by sodium triacetoxyborohydride (23.4 mg, 16.3 µL, 2 Eq, 110 µmol). The mixture was stirred at room temperature for 50 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50%Acetonitrile/ 0.05% Formic acid)) to afford (S)-3-((R)-7-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (30.71 mg, 38.68 µmol, 70.2 %) as white solid. LC-MS purity: 100% (UV at 254 nm), 794.6 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.38 (s, 1H), 7.25 – 7.15 (m, 6H), 6.98 (dd, J = 19.6, 7.6 Hz, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.60 (s, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.03 (dd, J = 13.2, 4.8 Hz, 1H), 4.30 (dd, J = 34.4, 13.2 Hz, 2H), 4.09 (d, J = 16.8 Hz, 2H), 3.95 (t, J = 9.6 Hz, 1H), 3.80 (d, J = 12.4 Hz, 1H), 3.55 – 3.43 (m, 6H), 3.24 – 3.08 (m, 2H), 2.96 – 2.85 (m, 4H), 2.75 – 2.56 (m, 2H), 2.42 – 2.37 (m, 2H), 2.16 – 1.86 (m, 6H), 1.75 (dd, J = 26.2, 15.1 Hz, 2H), 1.43 (dd, J = 31.0, 21.4 Hz, 6H).

Compound A140: (S)-3-((R)-7-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

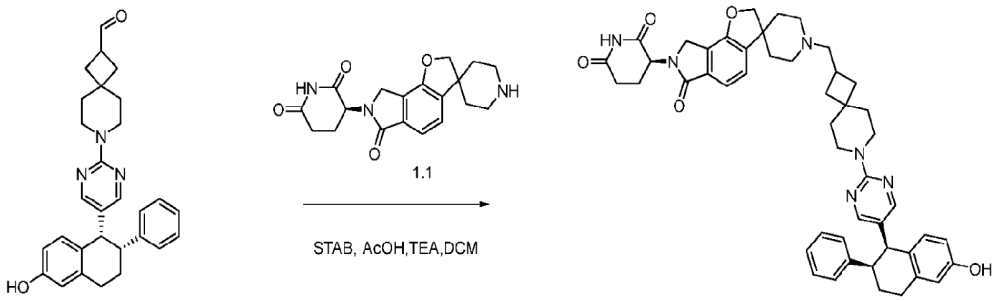


[0705] To a mixture of 7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonane-2-carbaldehyde (25.0 mg, 1 Eq, 55.1 µmol), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (23.6 mg, 1.2 Eq, 66.1 µmol), TEA (10.6 mg, 0.13 mmol, 1.5 eq.) in DCM (8.0 mL) was added acetic acid (7.6 mg, 0.11 mmol, 1.8 eq.) followed by sodium triacetoxyborohydride (23.4 mg, 16.3 µL, 2 Eq, 110 µmol). The mixture was stirred at room temperature for 50 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-((R)-7-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (24.66 mg, 31.06 µmol, 56.4 %)as white solid. LC-MS purity: 100% (UV at 254 nm),794.5 $[M+H]^+$.

[0706] ^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.31 (s, 1H), 7.25 – 7.16 (m, 6H), 6.97 (dd, J = 19.6, 7.6 Hz, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 6.52 (dd, J = 8.4, 2.4 Hz, 1H), 5.03

(dd, J = 13.2, 5.2 Hz, 1H), 4.30 (dd, J = 33.6, 12.8 Hz, 2H), 4.13 – 4.07 (m, 2H), 3.98 – 3.82 (m, 2H), 3.50 (d, J = 36.4 Hz, 6H), 2.94 – 2.84 (m, 4H), 2.68 (dd, J = 34.4, 23.4 Hz, 2H), 2.42 (dd, J = 26.7, 9.0 Hz, 4H), 2.13 – 1.69 (m, 8H), 1.43 (dd, J = 30.5, 20.8 Hz, 6H).

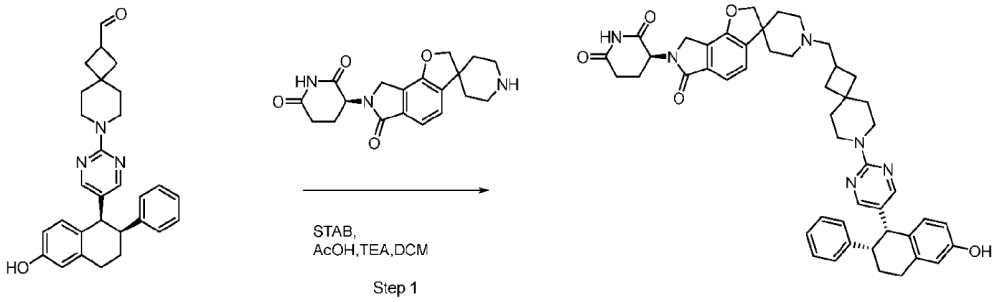
Compound A141: (S)-3-(1'-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0707] To a mixture of 7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonane-2-carbaldehyde (25.0 mg, 1 Eq, 55.1 µmol), (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (23.5 mg, 1.2 Eq, 66.1 µmol), TEA (10.6 mg, 0.13 mmol, 1.5 eq.) in DCM (8.0 mL) was added acetic acid (7.6 mg, 0.11 mmol, 1.8 eq.) followed by sodium triacetoxyhydroborate (23.4 mg, 2 Eq, 110 µmol). The mixture was stirred at room temperature for 50 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (24.06 mg, 30.34 µmol, 55.0 %)as white solid. LC-MS purity: 100% (UV at 254 nm),793.6 $[M+H]^+$.

[0708] ^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 8.25 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.21 (dt, J = 14.8, 8.2 Hz, 6H), 6.95 (d, J = 7.2 Hz, 2H), 6.70 (d, J = 8.4 Hz, 1H), 6.60 (s, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.08 (dd, J = 13.2, 4.8 Hz, 1H), 4.51 (s, 2H), 4.37 (d, J = 17.2 Hz, 1H), 4.20 (d, J = 17.2 Hz, 1H), 4.11 (d, J = 4.8 Hz, 1H), 3.56 – 3.44 (m, 6H), 3.04 – 2.66 (m, 6H), 2.46 – 2.32 (m, 4H), 2.02 – 1.85 (m, 8H), 1.65 (t, J = 10.4 Hz, 2H), 1.52 – 1.34 (m, 6H).

Compound A142: (S)-3-(1'-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

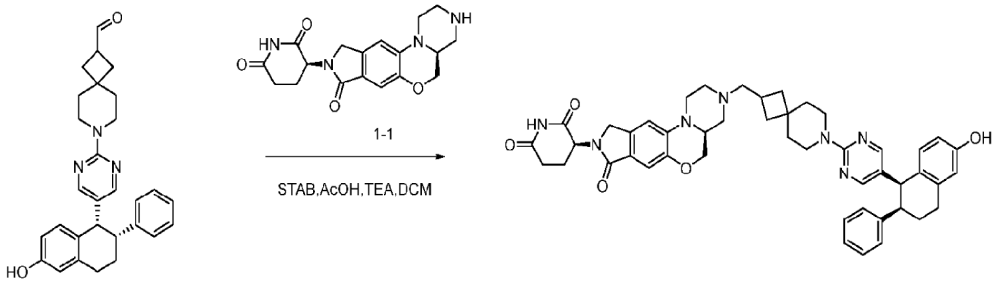


[0709] To a mixture of 7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonane-2-carbaldehyde (25.0 mg, 1 Eq, 55.1 µmol), (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (23.5 mg, 1.2 Eq, 66.1 µmol), TEA (10.6 mg, 0.13 mmol, 1.5 eq.) in DCM (8.0 mL) was added acetic acid (7.6 mg, 0.11 mmol, 1.8 eq.) followed by Sodium triacetoxyborohydride (23.4 mg, 16.3 µL, 2 Eq, 110 µmol). The mixture was stirred at room temperature for 50 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (32.89 mg, 41.48 µmol, 75.3 %)as white solid.
LC-MS purity: 100% (UV at 254 nm),793.6 $[M+H]^+$.

[0710] ^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.38 (s, 1H), 7.25 – 7.15 (m, 6H), 6.98 (dd, J = 19.6, 7.6 Hz, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.60 (s, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.30 (dd, J = 34.0, 13.2 Hz, 2H), 4.09 (d, J = 16.8 Hz, 2H), 3.95 (t, J = 9.6 Hz, 1H), 3.83 – 3.77 (m, 1H), 3.56 – 3.47 (m, 4H), 3.37 – 3.31 (m, 2H), 3.15 (s, 2H), 2.94 – 2.83 (m, 4H), 2.75 – 2.56 (m, 2H), 2.45 – 2.36 (m, 3H), 2.18 – 1.85 (m, 6H), 1.82 – 1.69 (m, 2H), 1.51 – 1.34 (m, 6H).

Compound A143: (S)-3-((S)-3-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-

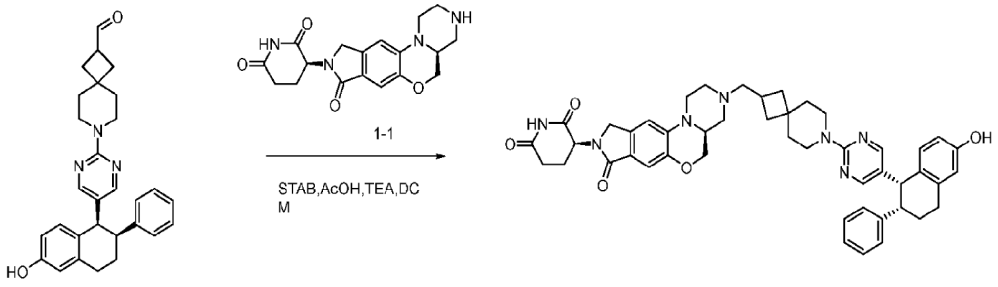
1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0711] To a mixture of 7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonane-2-carbaldehyde (25.0 mg, 1 Eq, 55.1 µmol), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (23.6 mg, 1.2 Eq, 66.1 µmol), TEA (10.6 mg, 0.13 mmol, 1.5 eq.) in DCM (8.0 mL) was added acetic acid (7.6 mg, 0.11 mmol, 1.8 eq.) followed by sodium triacetoxyhydroborate (23.4 mg, 2 Eq, 110 µmol). The mixture was stirred at room temperature for 50 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-((S)-3-((7-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (22.97 mg, 28.93 µmol, 52.5 %)as white solid. LC-MS purity: 100% (UV at 254 nm),794.5 $[M+H]^+$.

[0712] ^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.26 – 7.16 (m, 5H), 7.03 (s, 1H), 6.98 – 6.92 (m, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.02 (dd, J = 13.2, 4.8 Hz, 1H), 4.38 – 4.04 (m, 5H), 3.94 – 3.74 (m, 3H), 3.14 (s, 2H), 3.04 – 2.82 (m, 6H), 2.78 – 2.54 (m, 3H), 2.47 – 2.29 (m, 4H), 2.14 – 1.68 (m, 8H), 1.53 – 1.35 (m, 6H).

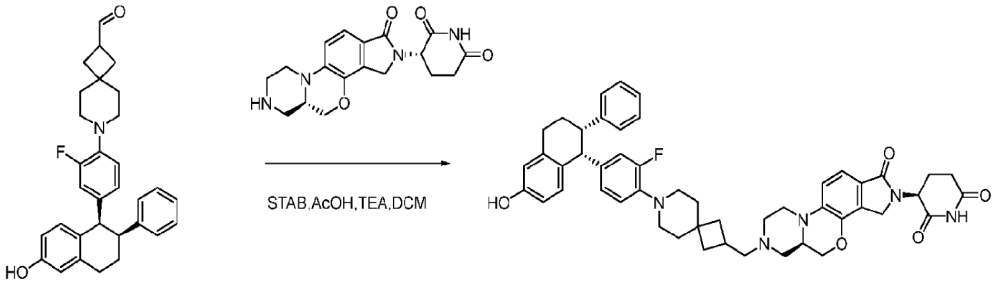
Compound A144: (S)-3-((S)-3-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0713] To a mixture of 7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonane-2-carbaldehyde (25.0 mg, 1 Eq, 55.1 µmol), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (19.6 mg, 1 Eq, 55.1 µmol), TEA (10.6 mg, 0.13 mmol, 1.5 eq.) in DCM (8.0 mL) was added acetic acid (7.6 mg, 0.11 mmol, 1.8 eq.) followed by sodium triacetoxyhydroborate (23.4 mg, 2 Eq, 110 µmol). The mixture was stirred at room temperature for 50 minutes and concentrated. The residue was purified by reverse-phase chromatography (0 acetonitrile/ 0.05% formic acid) to afford (S)-3-((S)-3-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (26.58 mg, 33.48 µmol, 60.7 %)as white solid. LC-MS purity: 100% (UV at 254 nm),794.7 $[M+H]^+$.

[0714] ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.18 (s, 1H), 7.26 – 7.16 (m, 5H), 7.03 (s, 1H), 6.98 – 6.91 (m, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 8.4, 2.4 Hz, 1H), 5.02 (dd, J = 13.2, 4.8 Hz, 1H), 4.29 – 4.09 (m, 4H), 3.92 – 3.86 (m, 1H), 3.78 (d, J = 11.2 Hz, 1H), 3.58 – 3.43 (m, 6H), 3.24 – 3.05 (m, 2H), 2.99 – 2.84 (m, 5H), 2.78 – 2.69 (m, 1H), 2.44 – 2.29 (m, 3H), 2.13 – 1.91 (m, 5H), 1.82 – 1.66 (m, 2H), 1.51 – 1.34 (m, 6H).

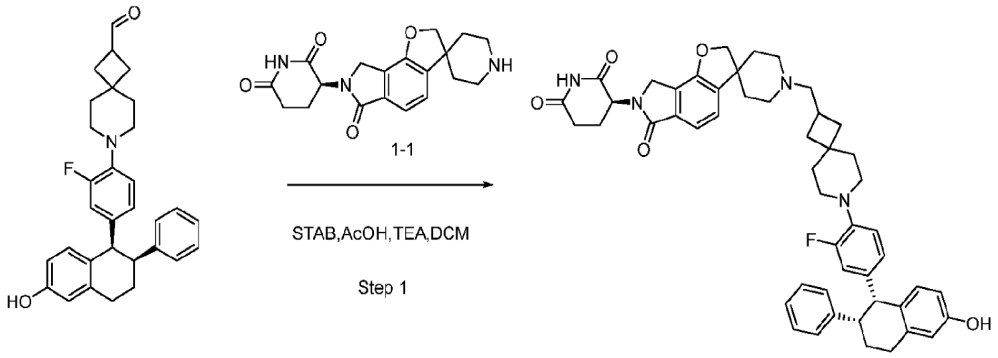
Compound A145: (S)-3-((R)-7-((7-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0715] To a mixture of 7-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (28.0 mg, 1 Eq, 59.6 µmol), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (25.5 mg, 1.2 Eq, 71.6 µmol), TEA (10.6 mg, 0.13 mmol, 1.5 eq.) in DCM (8.0 mL) was added acetic acid (7.6 mg, 0.11 mmol, 1.8 eq.) followed by sodium triacetoxyhydroborate (25.3 mg, 2 Eq, 119 µmol). The mixture was stirred at room temperature for 50 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50%Acetonitrile/ 0.05% Formic acid)) to afford (S)-3-((R)-7-((7-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (40.82 mg, 50.40 µmol, 84.5 %)as white solid. LC-MS purity: 100% (UV at 254 nm),810.4 $[M+H]^+$.

[0716] ^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.26 (s, 1H), 7.20 – 6.98 (m, 5H), 6.86 – 6.78 (m, 2H), 6.61 (d, J = 8.8 Hz, 2H), 6.55 – 6.42 (m, 3H), 6.25 (d, J = 13.6 Hz, 1H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.47 – 4.22 (m, 3H), 4.10 (d, J = 16.8 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.80 (d, J = 11.2 Hz, 1H), 3.22 – 3.10 (m, 2H), 3.03 – 2.84 (m, 9H), 2.76 – 2.58 (m, 2H), 2.49 – 2.33 (m, 4H), 2.22 – 2.06 (m, 2H), 1.99 – 1.86 (m, 3H), 1.76 – 1.57 (m, 4H), 1.52 – 1.37 (m, 4H).

Compound A146: (S)-3-(1'-((7-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



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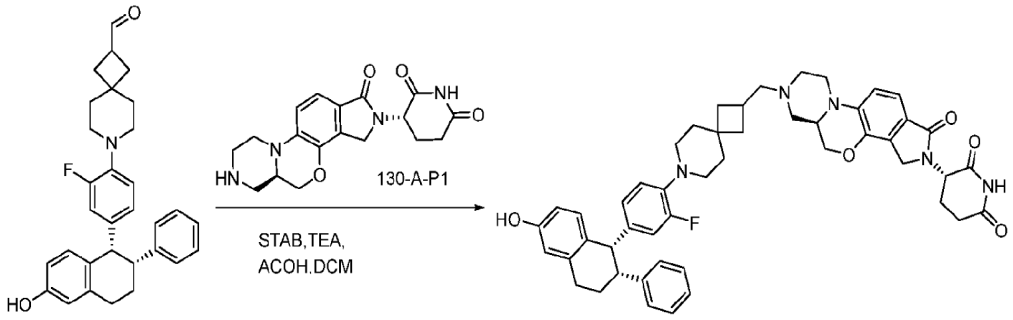
[0717] To a mixture of 7-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (30.0 mg, 1 Eq, 63.9 μmol), (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (27.2 mg, 1.2 Eq, 76.7 μmol), TEA (10.6 mg, 0.13 mmol, 1.5 eq.) in DCM (8.0 mL) was added acetic acid (7.6 mg, 0.11 mmol, 1.8 eq.) followed by sodium triacetoxyhydroborate (27.1 mg, 2 Eq, 128 μmol). The mixture was stirred at room temperature for 50 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((7-(2-fluoro-4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (47.69 mg, 58.95 μmol, 92.3 %)as white solid. LC-MS purity: 99.5% (UV at 254 nm),809.8 $[M+H]^+$.

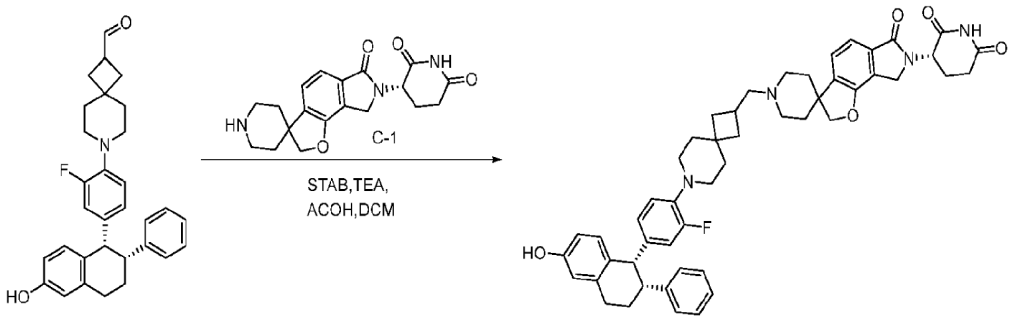
[0718] ^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 8.31 (s, 1H), 7.32 (dd, J = 47.6, 7.6 Hz, 2H), 7.13 – 7.07 (m, 3H), 6.85 – 6.79 (m, 2H), 6.63 – 6.45 (m, 5H), 6.25 (d, J = 12.8 Hz, 1H), 5.08 (dd, J = 13.2, 4.8 Hz, 1H), 4.57 – 4.33 (m, 4H), 4.21 (d, J = 17.2 Hz, 1H), 3.05 – 2.85 (m, 8H), 2.65 – 2.53 (m, 2H), 2.47 – 2.33 (m, 4H), 2.10 – 1.81 (m, 8H), 1.74 – 1.36 (m, 10H).

Compound A147: (S)-3-((R)-7-((7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



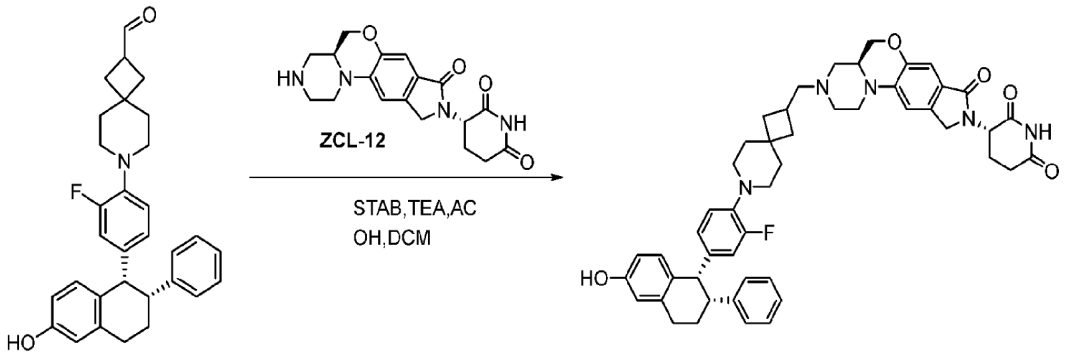
[0719] To a mixture of 7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (33.5 m g, 0.071 mmol 1 eq.), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (27.72 mg, 0.078 mmol 1.1eq.) TEA (10.7 mg, 0.106 mmol, 1.5 eq.) in DCM (2 mL),) was added acetic acid (7.2 mg, 0.12 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (30.0 mg,0.14 mmol 2.0 eq.) The resultant mixture was then stirred at 25°C for 2h. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((R)-7-((7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (32.01 mg, 55.9 % yield) as a white solid. LC-MS (ESI, m/z): mass calcd. For $C_{50}H_{55}N_5O_6$, 821.42; found, 822.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.14 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.11 – 7.07 (m, 3H), 7.00 (d, J = 8.5 Hz, 1H), 6.84 – 6.78 (m, 2H), 6.64 – 6.56 (m, 2H), 6.55 – 6.41 (m, 3H), 6.25 (d, J = 13.6 Hz, 1H), 5.07 – 4.99 (m, 1H), 4.47 – 4.40 (m, 1H), 4.38 – 4.30 (m, 1H), 4.30 – 4.20 (m, 1H), 4.13 – 4.04 (m, 1H), 4.00 – 3.89 (m, 1H), 3.84 – 3.76 (m, 1H), 3.19 – 3.09 (m, 2H), 3.06 – 2.82 (m, 10H), 2.75 – 2.67 (m, 1H), 2.63 – 2.54 (m, 1H), 2.43 – 2.36 (m, 3H), 2.22 – 2.05 (m, 2H), 1.98 – 1.88 (m, 3H), 1.79 – 1.58 (m, 4H), 1.52 – 1.38 (m, 4H).

Compound A148: (S)-3-(1'-((7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0720] To a mixture of 7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (28.2 mg, 0.060 mmol 1 eq.), (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (23.43 mg, 0.066 mmol 1.1eq.) TEA (9.1 mg, 0.09 mmol, 1.5 eq.) in DCM (2 mL) was added acetic acid (6.12 mg, 0.10 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (25.44 mg,0.12 mmol 2.0 eq.) The resultant mixture was then stirred at 25°C for 2h. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (28.81 mg, 59.4 % yield) as a white solid. LC-MS (ESI, m/z): mass calcd. For $C_{50}H_{55}N_5O_6$, 821.42; found, 822.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.13 (s, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.13 – 7.06 (m, 3H), 6.84 – 6.79 (m, 2H), 6.64 – 6.57 (m, 2H), 6.55 – 6.42 (m, 3H), 6.26 (d, J = 13.6 Hz, 1H), 5.12 – 5.04 (m, 1H), 4.56 – 4.48 (m, 2H), 4.47 – 4.42 (m, 1H), 4.41 – 4.33 (m, 1H), 4.24 – 4.16 (m, 1H), 3.04 – 2.80 (m, 10H), 2.68 – 2.55 (m, 2H), 2.47 – 2.36 (m, 3H), 2.23 – 2.13 (m, 1H), 2.09 – 1.83 (m, 7H), 1.74 – 1.56 (m, 5H), 1.54 – 1.36 (m, 4H).

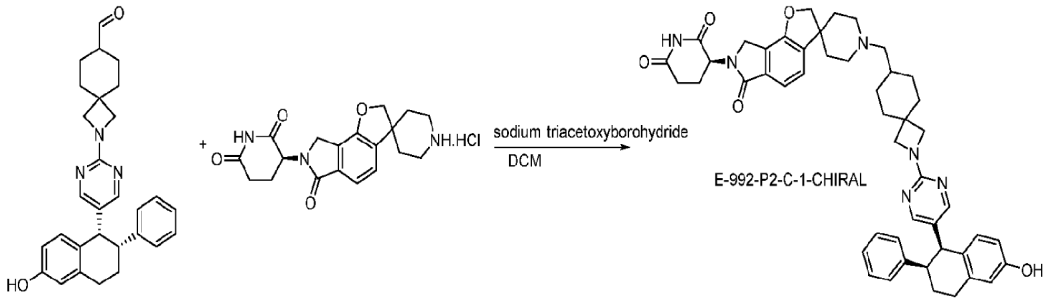
Compound A149: (S)-3-((S)-3-((7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0721] To a mixture of 7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (26.5 mg, 0.057mmol 1 eq.), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (22.13 mg, 0.062 mmol 1.1eq.) TEA (8.6 mg, 0.085 mmol, 1.5 eq.) in DCM (2 mL) was added acetic acid (5.8 mg, 0.09 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (23.96 mg,0.11 mmol 2.0 eq.) The resultant mixture was then stirred at 25°C. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((S)-3-((7-(2-fluoro-4-((1S,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (28.81 mg, 59.4 % yield) as a white solid. LC-MS (ESI, m/z): mass calcd. For $C_{50}H_{55}N_5O_6$, 821.42; found, 822.4 $[M+H]^+$.

[0722] ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.24 – 9.09 (m, 1H), 7.15 – 7.00 (m, 4H), 6.93 (s, 1H), 6.85 – 6.76 (m, 2H), 6.64 – 6.57 (m, 2H), 6.56 – 6.41 (m, 3H), 6.31 – 6.21 (m, 1H), 5.07 – 4.98 (m, 1H), 4.44 (d, J = 5.2 Hz, 1H), 4.32 – 4.09 (m, 3H), 3.92 – 3.75 (m, 2H), 3.18 – 3.08 (m, 2H), 3.07 – 2.81 (m, 10H), 2.79 – 2.63 (m, 1H), 2.63 – 2.56 (m, 1H), 2.43 – 2.27 (m, 3H), 2.25 – 2.03 (m, 2H), 2.02 – 1.86 (m, 3H), 1.76 – 1.55 (m, 4H), 1.52 – 1.34 (m, 4H).

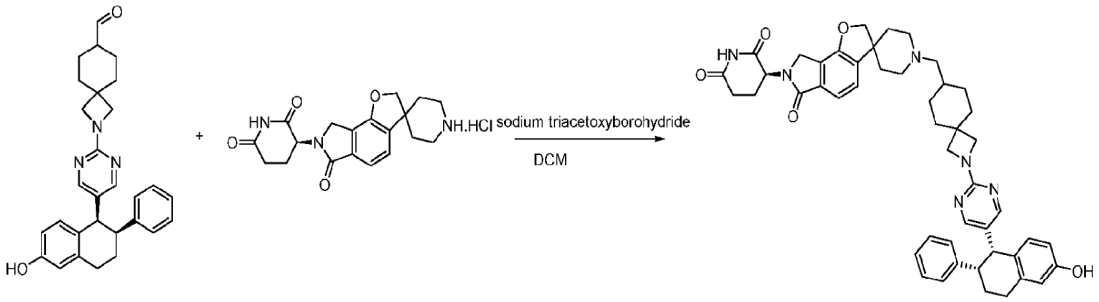
Compound A153: (S)-3-(1'-((2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0723] To a mixture of 2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30.0 mg, 66.1 µmol, 1 eq.), (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione hydrochloride (31.1 mg, , 79.4 µmol, 1.2 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (22.64 mg, 28.55 µmol, 43.2 %) as a white solid. LC-MS purity: 99.8% (UV at 254 nm), 793.3 $[M+H]^+$.

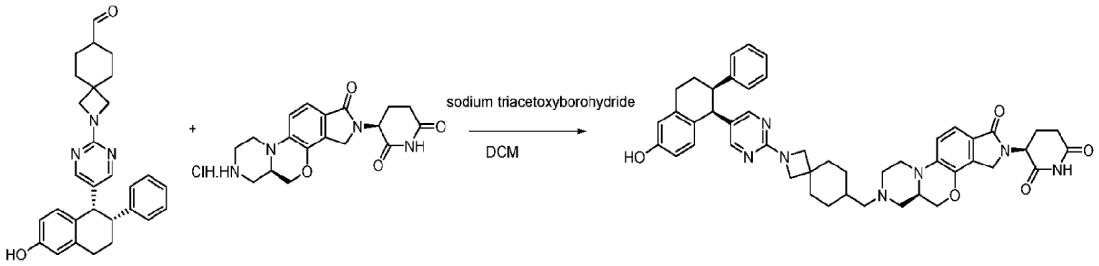
[0724] ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.30 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.28 – 7.15 (m, 6H), 6.95 (d, J = 7.2 Hz, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 6.53 – 6.48 (m, 1H), 5.12 – 5.05 (m, 1H), 4.54 – 4.48 (m, 2H), 4.41 – 4.34 (m, 1H), 4.24 – 4.17 (m, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.57 (s, 2H), 3.52 (s, 2H), 3.37 – 3.31 (m, 2H), 3.01 – 2.87 (m, 3H), 2.82 – 2.76 (m, 2H), 2.63 – 2.53 (m, 1H), 2.44 – 2.33 (m, 1H), 2.10 (d, J = 6.8 Hz, 2H), 2.01 – 1.86 (m, 6H), 1.81 (d, J = 12.0 Hz, 3H), 1.72 – 1.62 (m, 4H), 1.52 – 1.35 (m, 3H), 0.98 – 0.83 (m, 2H).

Compound A154: (S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0725] To a mixture of 2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30.0 mg, 66.1 µmol, 1 eq.), (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione hydrochloride (31.1 mg, , 79.4 µmol, 1.2 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (22.64 mg, 28.55 µmol, 43.2 %) as a white solid. LC-MS purity: 99.8% (UV at 254 nm), 793.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.26 (s, 1H), 7.44 – 7.36 (m, 1H), 7.26 – 7.15 (m, 6H), 6.95 (d, J = 7.2 Hz, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 6.54 – 6.48 (m, 1H), 5.13 – 5.04 (m, 1H), 4.50 (t, J = 10.2 Hz, 2H), 4.40 – 4.34 (m, 1H), 4.24 – 4.17 (m, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.57 (s, 2H), 3.52 (s, 2H), 3.36 – 3.29 (m, 2H), 3.00 – 2.86 (m, 3H), 2.82 – 2.75 (m, 2H), 2.66 – 2.54 (m, 1H), 2.47 – 2.34 (m, 1H), 2.10 (d, J = 6.8 Hz, 2H), 2.00 – 1.86 (m, 6H), 1.84 – 1.75 (m, 3H), 1.72 – 1.61 (m, 4H), 1.51 – 1.36 (m, 3H), 0.95 – 0.82 (m, 2H).

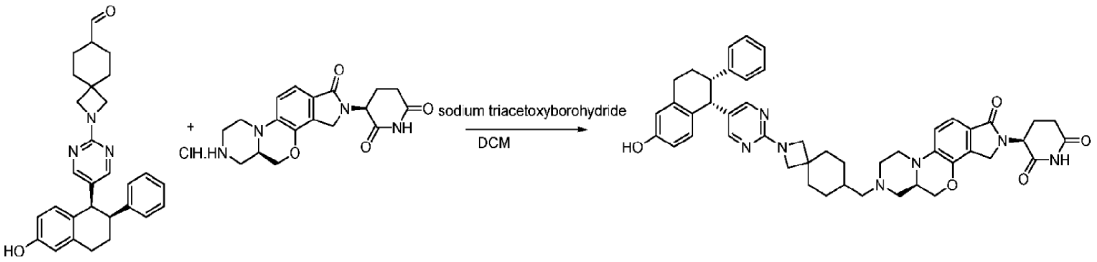
Compound A155: (S)-3-((R)-7-((2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0726] To a mixture of 2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30.0 mg, 66.1 µmol, 1 eq.), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride (31.1 mg, , 79.4 µmol, 1.2 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL)was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((R)-7-((2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (25.32 mg, 31.89 µmol, 48.2 %) as a white solid. LC-MS purity: 92.2% (UV at 254 nm), 794.4 $[M+H]^+$.

[0727] ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.28 – 7.15 (m, 6H), 7.02 – 6.91 (m, 3H), 6.68 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 6.53 – 6.46 (m, 1H), 5.08 – 4.96 (m, 1H), 4.39 – 4.33 (m, 1H), 4.29 – 4.21 (m, 1H), 4.15 – 4.06 (m, 2H), 3.99 – 3.91 (m, 1H), 3.81 (d, J = 10.8 Hz, 1H), 3.56 – 3.51 (m, 3H), 3.36 – 3.30 (m, 1H), 3.19 – 3.14 (m, 1H), 3.00 – 2.84 (m, 5H), 2.76 – 2.59 (m, 2H), 2.59 – 2.53 (m, 1H), 2.43 – 2.34 (m, 1H), 2.17 – 2.02 (m, 3H), 1.99 – 1.91 (m, 2H), 1.83 – 1.76 (m, 3H), 1.73 – 1.62 (m, 3H), 1.53 – 1.36 (m, 3H), 1.01 (t, J = 7.2 Hz, 1H), 0.97 – 0.82 (m, 2H).

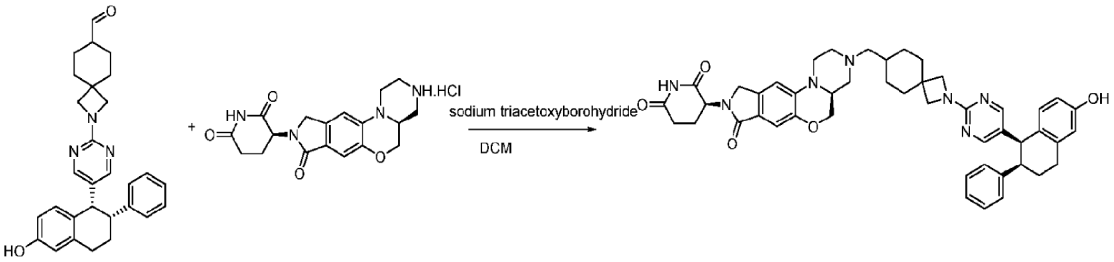
Compound A156: (S)-3-((R)-7-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0728] To a mixture of 1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidine-4-carbaldehyde (30.0 mg, 66.1 µmol, 1 eq.), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride (31.1 mg, , 79.4 µmol, 1.2 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((R)-7-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (25.32 mg, 31.89 µmol, 48.2 %) as a white solid. LC-MS purity: 92.2% (UV at 254 nm), 794.3 $[M+H]^+$.

[0729] ^{1}H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 7.31 – 7.22 (m, 6H), 7.07 – 6.94 (m, 3H), 6.74 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 2.0 Hz, 1H), 6.59 – 6.53 (m, 1H), 5.13 – 5.03 (m, 1H), 4.45 – 4.37 (m, 1H), 4.34 – 4.27 (m, 1H), 4.22 – 4.11 (m, 2H), 4.05 – 3.98 (m, 1H), 3.89 – 3.84 (m, 1H), 3.63 – 3.60 (m, 2H), 3.58 (s, 3H), 3.24 – 3.19 (m, 1H), 3.13 – 2.86 (m, 6H), 2.79 (t, J = 10.4 Hz, 1H), 2.68 – 2.58 (m, 1H), 2.51 – 2.38 (m, 1H), 2.24 – 2.08 (m, 3H), 2.05 – 1.95 (m, 2H), 1.89 – 1.81 (m, 3H), 1.79 – 1.69 (m, 3H), 1.58 – 1.42 (m, 3H), 1.03 – 0.87 (m, 2H).

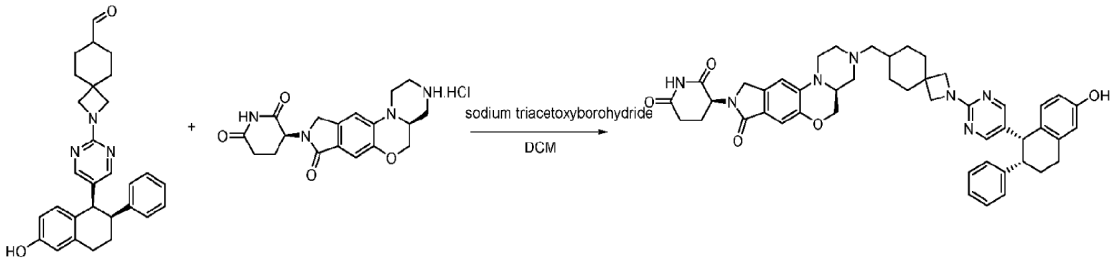
Compound A157: (S)-3-((S)-3-((2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0730] To a mixture of 2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30.0 mg, 66.1 µmol, 1 eq.), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride (31.1 mg, , 79.4 µmol, 1.2 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL)was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((S)-3-((2-(5-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (20.53 mg, 25.86 µmol, 39.1 %) as a white solid. LC-MS purity: 92.2% (UV at 254 nm), 794.4 $[M+H]^+$.

[0731] ^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.26 – 7.15 (m, 5H), 7.03 (s, 1H), 6.94 (d, J = 6.6 Hz, 3H), 6.68 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 6.55 – 6.47 (m, 1H), 5.06 – 4.97 (m, 1H), 4.32 – 4.20 (m, 2H), 4.17 – 4.07 (m, 2H), 3.97 – 3.82 (m, 2H), 3.81 – 3.72 (m, 2H), 3.37 – 3.30 (m, 2H), 3.19 – 3.01 (m, 2H), 3.02 – 2.80 (m, 6H), 2.75 (t, J = 10.4 Hz, 1H), 2.61 – 2.54 (m, 1H), 2.41 – 2.28 (m, 1H), 2.16 – 2.03 (m, 3H), 2.00 – 1.90 (m, 2H), 1.84 – 1.74 (m, 3H), 1.72 – 1.61 (m, 3H), 1.53 – 1.36 (m, 3H), 0.98 – 0.84 (m, 2H).

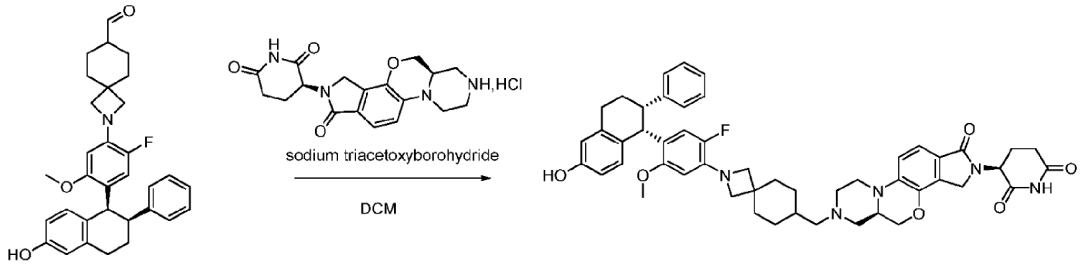
Compound A158: (S)-3-((S)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0732] To a mixture of 2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30.0 mg, 66.1 μmol, 1 eq.) (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride (31.1 mg, , 79.4 μmol, 1.2 eq.) and TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.00 mL)was addedacetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was by Prep-HPLC (Acetonitrile/ 0.05% Formate acid) to afford (S)-3-((S)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (17.82 mg, 22.44 μmol, 33.9 %) as a white solid. LC-MS purity: 99.8% (UV at 254 nm), 794.3 $[M+H]^+$.

[0733] ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.31 (s, 1H), 7.25 – 7.12 (m, 5H), 7.03 (s, 1H), 6.97 – 6.88 (m, 3H), 6.68 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 6.53 – 6.44 (m, 1H), 5.06 – 4.98 (m, 1H), 4.33 – 4.19 (m, 2H), 4.18 – 4.08 (m, 2H), 3.92 – 3.75 (m, 3H), 3.58 – 3.55 (m, 2H), 3.36 – 3.32 (m, 1H), 3.17 – 3.12 (m, 1H), 3.00 – 2.85 (m, 5H), 2.79 – 2.70 (m, 1H), 2.66 – 2.51 (m, 2H), 2.40 – 2.30 (m, 1H), 2.19 – 2.02 (m, 3H), 1.99 – 1.89 (m, 2H), 1.84 – 1.75 (m, 3H), 1.74 – 1.63 (m, 3H), 1.53 – 1.36 (m, 3H), 1.06 – 0.97 (m, 1H), 0.95 – 0.83 (m, 2H).

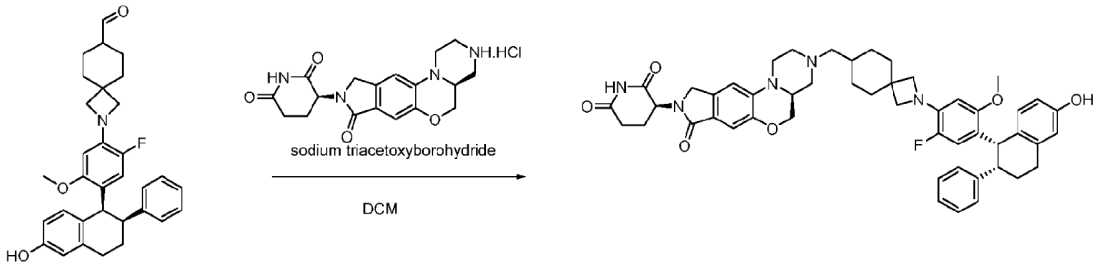
Compound A163: (S)-3-((R)-7-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione.



[0734] To a mixture of 2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (0.03 g, 1.0 eq, 0.06 mmol), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (0.02 g, 1.1 eq, 0.07 mmol) in DCM (5.00 mL) was added sodium triacetoxyborohydride (0.03 g, 0.02 mL, 2.0 eq, 0.1 mmol). The resultant mixture was then stirred at 25 °C for 1 h. The residue was purified by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((R)-7-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (28.88 mg, 60 % yield) as a white solid. LC-MS purity: 99.7 % (UV at 254 nm), 840.4 $[M+H]^+$.

[0735] ^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.11 (s, 1H), 7.22 – 6.95 (m, 5H), 6.78 (d, *J* = 6.8 Hz, 2H), 6.65 – 6.39 (m, 3H), 6.10 (d, *J* = 13.6 Hz, 1H), 5.67 (d, *J* = 8.0 Hz, 1H), 5.03 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.62 (d, *J* = 5.2 Hz, 1H), 4.40 – 4.31 (m, 1H), 4.18 (dd, *J* = 62.8, 16.8 Hz, 2H), 4.01 – 3.89 (m, 1H), 3.81 (d, *J* = 11.6 Hz, 1H), 3.57 – 3.45 (m, 4H), 3.23 – 3.14 (m, 2H), 3.02 – 2.82 (m, 8H), 2.74 (d, *J* = 10.4 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.43 – 2.31 (m, 1H), 2.20 – 2.01 (m, 4H), 1.99 – 1.84 (m, 3H), 1.76 – 1.58 (m, 4H), 1.55 – 1.37 (m, 3H), 1.00 – 0.82 (m, 2H).

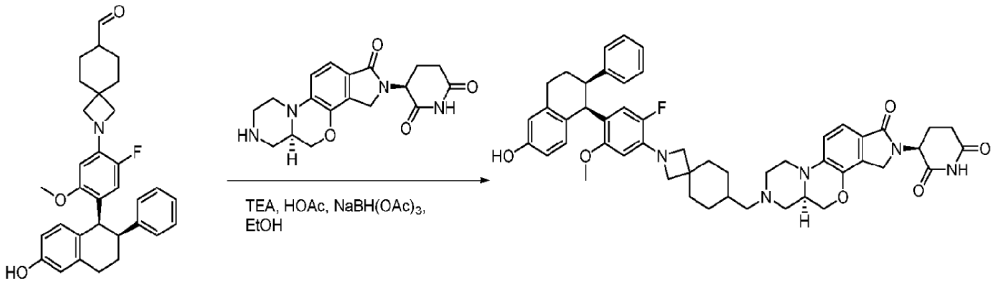
Compound A164: (S)-3-((S)-3-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0736] To a mixture of 2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (0.03 g, 1 eq, 0.06 mmol), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (0.02 g, 1.1 eq, 0.07 mmol) in DCM (5.00 mL) was added sodium triacetoxyborohydride (0.03 g, 0.02 mL, 2.0 eq, 0.1 mmol). The resultant mixture was then stirred at 25 °C for 1 h. The residue was purified by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-((S)-3-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (21.04 mg, 40 % yield) as a white solid. LC-MS purity: 99.7 % (UV at 254 nm), 840.4 $[M+H]^+$.

[0737] ^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.11 (s, 1H), 7.14 – 7.00 (m, 4H), 6.93 (s, 1H), 6.78 (d, *J* = 6.8 Hz, 2H), 6.60 – 6.43 (m, 3H), 6.10 (d, *J* = 13.6 Hz, 1H), 5.67 (d, *J* = 8.0 Hz, 1H), 5.02 (dd, *J* = 13.2, 4.8 Hz, 1H), 4.62 (d, *J* = 5.2 Hz, 1H), 4.32 – 4.11 (m, 3H), 3.93 – 3.76 (m, 2H), 3.57 – 3.45 (m, 4H), 3.24 – 3.14 (m, 2H), 2.98 – 2.84 (m, 8H), 2.80 – 2.72 (m, 1H), 2.64 – 2.57 (m, 1H), 2.39 – 2.30 (m, 1H), 2.17 – 2.07 (m, 3H), 1.98 – 1.84 (m, 3H), 1.75 – 1.59 (m, 4H), 1.54 – 1.38 (m, 3H), 1.24 (s, 1H), 0.98 – 0.85 (m, 2H).

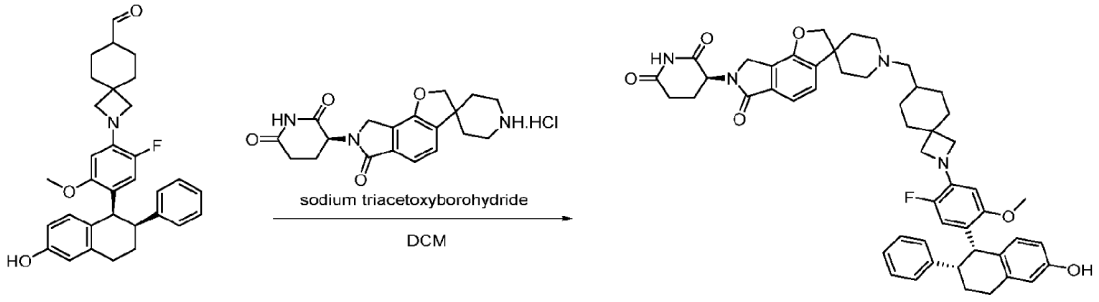
Compound A165: (S)-3-((R)-7-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0738] To a mixture of 72-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), (S)-2-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yl)-3,5-dihydro-1H-pyrrolo[3,4-c]pyridine-1,4(2H)-dione (30 mg, 0.07 mmol, 1.2 eq.), TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-((R)-7-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.8% (UV at 254 nm), 840.4 $[M+H]^+$.

[0739] ^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 7.19 – 6.97 (m, 5H), 6.78 (d, J = 6.8 Hz, 2H), 6.64 – 6.46 (m, 3H), 6.10 (d, J = 13.6 Hz, 1H), 5.67 (d, J = 8.0 Hz, 1H), 5.07 – 4.93 (m, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.40 – 4.34 (m, 1H), 4.31 – 4.09 (m, 2H), 3.97 (d, J = 8.8 Hz, 1H), 3.86 – 3.79 (m, 1H), 3.62 – 3.46 (m, 5H), 3.29 – 3.07 (m, 5H), 2.91 (d, J = 10.6 Hz, 6H), 2.59 (s, 1H), 2.42 – 2.34 (m, 1H), 2.17 – 1.88 (m, 6H), 1.72 – 1.36 (m, 7H), 1.24 (s, 1H), 0.98 – 0.84 (m, 2H).

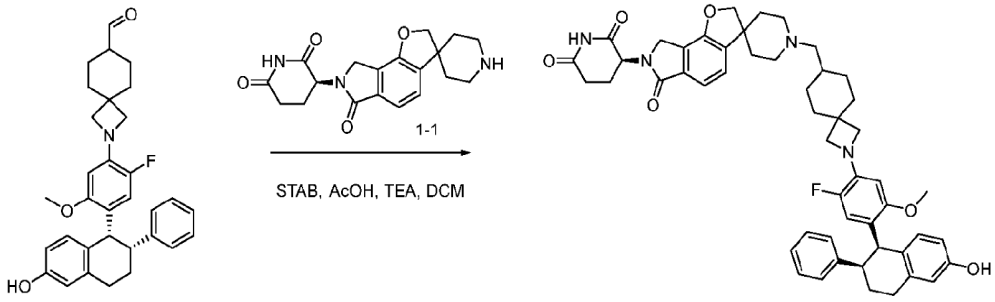
Compound A166: (S)-3-(1'-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione.



[0740] To a mixture of 2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (0.03 g, 1 eq, 0.06 mmol), (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione hydrochloride (0.02 g, 1.1 eq, 0.07 mmol) in DCM (5.00 mL) was added sodium triacetoxyborohydride (0.03 g, 0.02 mL, 2.0 eq, 0.1 mmol). The resultant mixture was then stirred at 25 °C for 1 h. The residue was purified by Prep-HPLC (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (25.5 mg, 50 % yield) as a white solid. LC-MS purity: 99.4 % (UV at 254 nm), 839.4 $[M+H]^+$.

[0741] ^{1}H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1 H), 8.26 (s, 1 H), 7.45 (s, 1 H), 7.12-7.02 (m, 3 H), 7.00 (s, 1 H), 6.78 (d, J=6.8 Hz, 2 H), 6.58-6.54 (m, 2 H), 6.49-6.46 (m, 1 H), 6.10 (d, J=13.6 Hz, 1 H), 5.67 (d, J=8.4 Hz, 1 H), 5.09-5.05 (m, 1 H), 4.63-4.62 (m, 1 H), 4.55 (s, 2 H), 4.34 (d, J=16.8 Hz, 1 H), 4.21 (d, J=17.2 Hz, 1 H), 3.57-3.46 (m, 4 H), 3.24-3.20 (m, 2 H), 2.93-2.78 (m, 8 H), 2.63-2.57 (m, 1 H), 2.43-2.31 (m, 1 H), 2.18-2.09 (m, 2 H), 2.00-1.86 (m, 7 H), 1.71-1.60 (m, 5 H), 1.52-1.40 (m, 3 H), 0.97-0.85 (m, 2 H)..

Compound A168: (S)-3-(1'-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

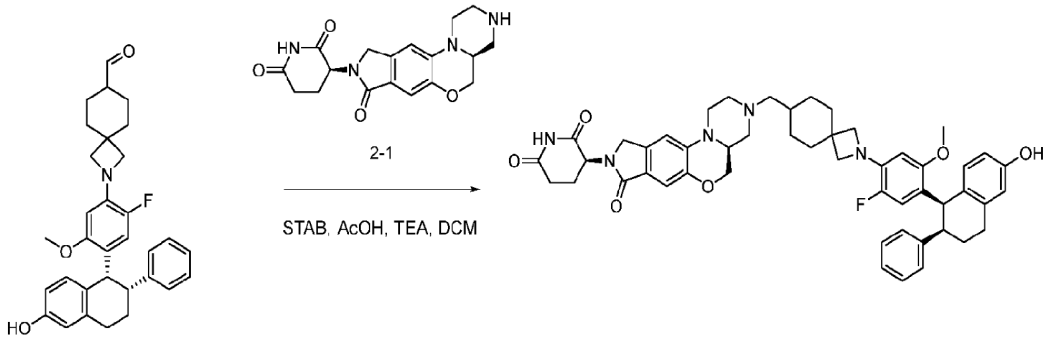


[0742] To a mixture of 2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (35.0 mg, 1 Eq, 70.1 μmol), (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (29.9 mg, 1.2 Eq, 84.1 μmol), TEA (10.6 mg, 0.13 mmol, 1.5 eq.) in DCM (4.0 mL) was added acetic acid (7.6 mg, 0.11 mmol, 1.8 eq.) followed by sodium

triacetoxyborohydride (29.7 mg, 20.8 µL, 2 Eq, 140 µmol). The mixture was stirred at room temperature for 50 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (25.84 mg, 30.80 µmol, 44.0 %) as white solid. LC-MS purity: 100% (UV at 254 nm),839.5 $[M+H]^+$.

[0743] ^{1}H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 9.56 – 8.58 (m, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.13 – 7.05 (m, 3H), 6.78 (d, J = 7.2 Hz, 2H), 6.59 – 6.53 (m, 2H), 6.50 – 6.45 (m, 1H), 6.10 (d, J = 13.2 Hz, 1H), 5.68 (d, J = 8.0 Hz, 1H), 5.08 (dd, J = 13.2, 4.8 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.51 (s, 2H), 4.38 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 3.22 (d, J = 14.4 Hz, 2H), 2.93 (s, 3H), 2.84 – 2.78 (m, 2H), 2.69 – 2.55 (m, 2H), 2.49 – 2.34 (m, 2H), 2.25 – 2.04 (m, 4H), 2.00 – 1.84 (m, 8H), 1.76 – 1.58 (m, 6H), 1.56 – 1.33 (m, 4H), 1.25 – 1.15 (m, 1H), 0.95 – 0.85 (m, 2H).

Compound A169: (S)-3-((S)-3-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

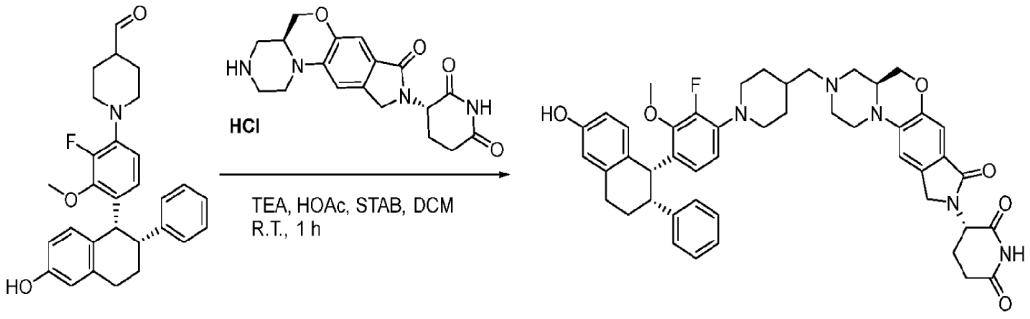


[0744] To a mixture of 2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (35.0 mg, 1 Eq, 70.1 µmol), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (30.0 mg, 1.2 Eq, 84.1 µmol), TEA (10.6 mg, 0.13 mmol, 1.5 eq.) in DCM (4.0 mL) was added acetic acid (7.6 mg, 0.11 mmol, 1.8 eq.) followed by sodium triacetoxyborohydride (29.7 mg, 20.8 µL, 2 Eq, 140 µmol).

The mixture was stirred at room temperature for 50 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-((S)-3-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (24.24 mg, 28.86 μmol, 41.2 %) as white solid. LC-MS purity: 100% (UV at 254 nm),840.5 $[M+H]^+$.

[0745] ^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.37 (s, 1H), 7.12 – 7.02 (m, 4H), 6.93 (s, 1H), 6.78 (d, J = 6.8 Hz, 2H), 6.60 – 6.53 (m, 2H), 6.48 (d, J = 8.4 Hz, 1H), 6.10 (d, J = 13.6 Hz, 1H), 5.67 (d, J = 8.0 Hz, 1H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.32 – 4.11 (m, 3H), 3.94 – 3.77 (m, 2H), 3.55 – 3.48 (m, 4H), 3.28 – 3.13 (m, 4H), 2.92 (s, 3H), 2.90 – 2.72 (m, 4H), 2.68 – 2.52 (m, 2H), 2.38 – 1.97 (m, 6H), 1.87 (d, J = 11.6 Hz, 2H), 1.74 – 1.59 (m, 4H), 1.47 – 1.39 (m, 2H), 0.97 – 0.85 (m, 2H).

Compound A170: (S)-3-((S)-3-((1-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

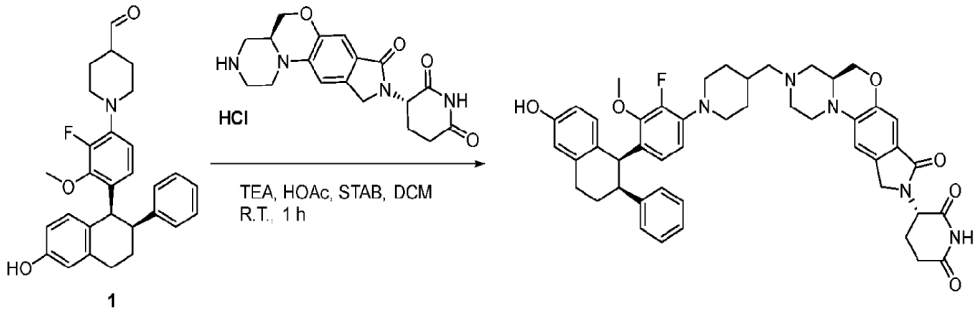


[0746] To a mixture of 1-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (30 mg, 0.065 mmol, 1 eq.), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride (31 mg, 0.078 mmol, 1.2 eq.), TEA (10 mg, 0.097 mmol, 1.5 eq.) in DCM (5.0 mL) was added acetic acid (7 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase

chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-((S)-3-((1-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (22.77 mg, 43.8% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 800.7 $[M+H]^+$.

[0747] ^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.15 – 7.02 (m, 4H), 6.94 (s, 1H), 6.77 (d, J = 6.6 Hz, 2H), 6.61 – 6.53 (m, 3H), 6.49 – 6.37 (m, 2H), 5.10 – 4.96 (m, 1H), 4.60 (d, J = 5.2 Hz, 1H), 4.33 – 4.10 (m, 3H), 3.93 – 3.76 (m, 2H), 3.31 – 3.12 (m, 5H), 3.02 – 2.85 (m, 8H), 2.82 – 2.73 (m, 1H), 2.64 – 2.52 (m, 3H), 2.41 – 2.16 (m, 4H), 2.14 – 2.05 (m, 1H), 2.00 – 1.91 (m, 1H), 1.84 – 1.59 (m, 5H), 1.32 – 1.17 (m, 2H).

Compound A171: (S)-3-((S)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



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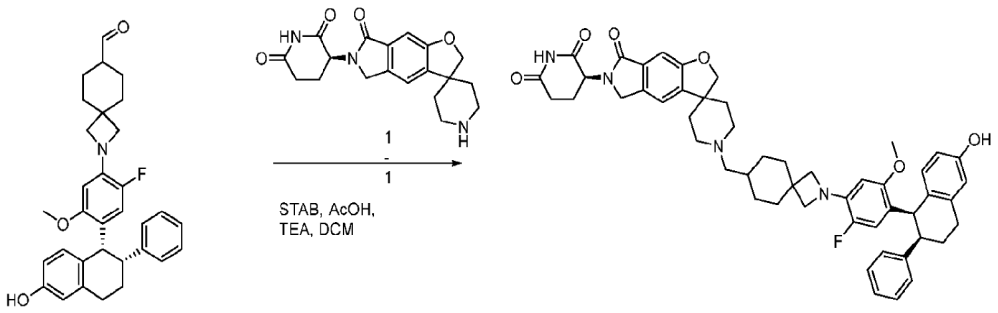
[0748] To a mixture of 1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (30 mg, 0.065 mmol, 1 eq.), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride (31 mg, 0.078 mmol, 1.2 eq.), TEA (10 mg, 0.097 mmol, 1.5 eq.) in DCM (5.0 mL) was added acetic acid (7 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-((S)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-

2,6-dione (25.01 mg, 48.1% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 800.7 $[M+H]^+$.

[0749] ^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.14 – 7.01 (m, 4H), 6.94 (s, 1H), 6.77 (d, *J* = 6.6 Hz, 2H), 6.61 – 6.53 (m, 3H), 6.49 – 6.38 (m, 2H), 5.08 – 4.96 (m, 1H), 4.60 (d, *J* = 5.4 Hz, 1H), 4.34 – 4.08 (m, 3H), 3.95 – 3.75 (m, 2H), 3.31 – 3.13 (m, 5H), 3.03 – 2.84 (m, 8H), 2.82 – 2.73 (m, 1H), 2.63 – 2.52 (m, 3H), 2.41 – 2.15 (m, 4H), 2.13 – 2.03 (m, 1H), 2.01 – 1.91 (m, 1H), 1.84 – 1.58 (m, 5H), 1.32 – 1.16 (m, 2H).

Compound A172: (S)-3-(1'-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

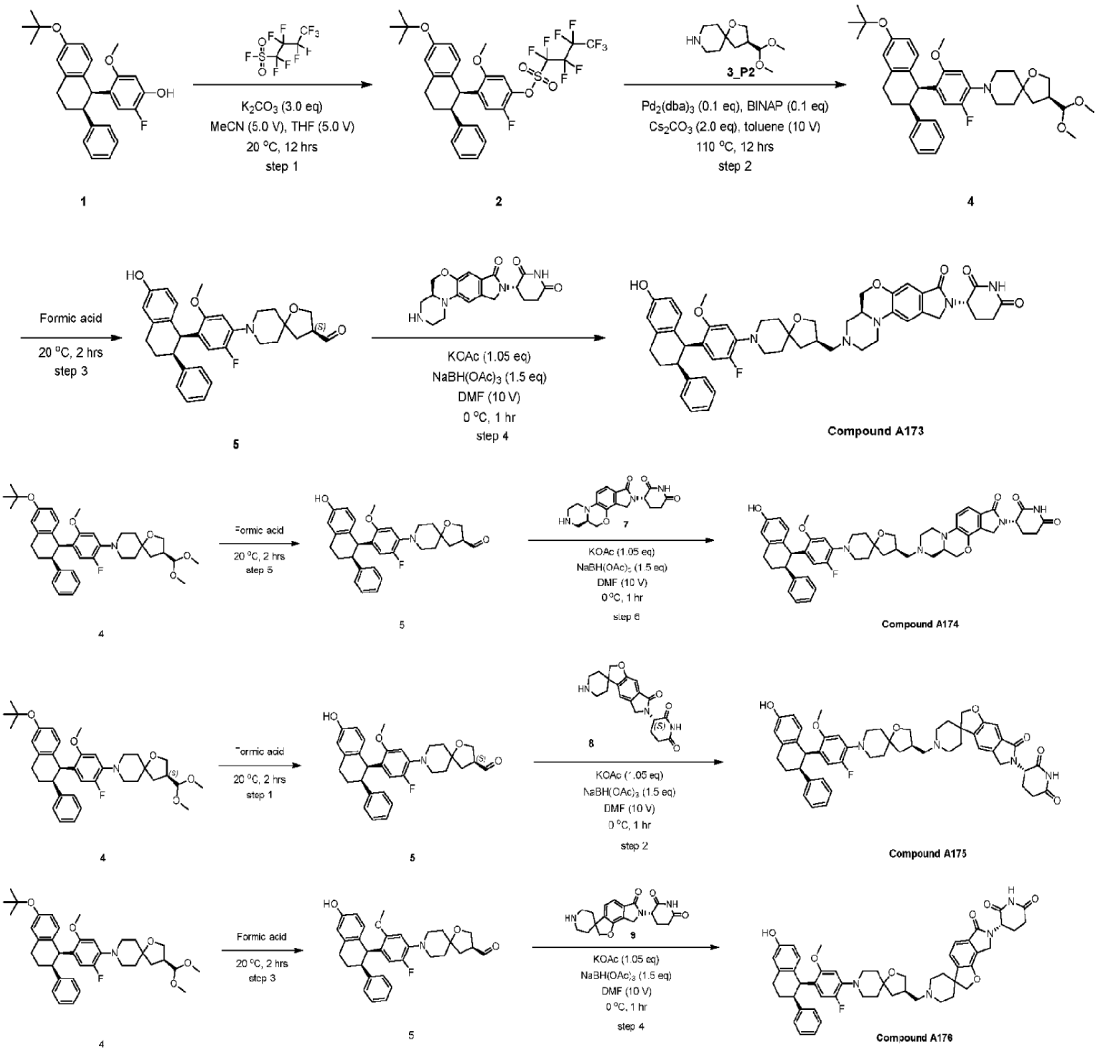


1 2

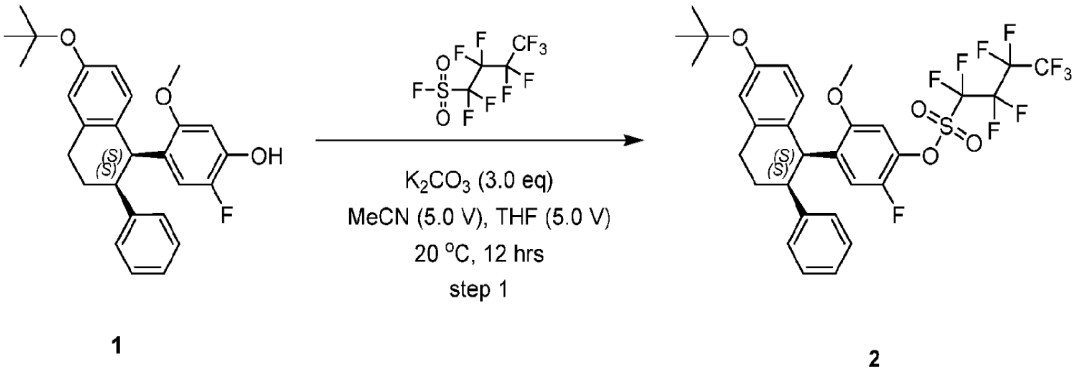
[0750] To a mixture of 2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (0.025 g, 1 Eq, 50 µmol), (S)-3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (21 mg, 1.2 Eq, 60 µmol), TEA (7.6 mg, 0.075 mmol, 1.5 eq.) in DCM (4.0 mL) was added acetic acid (5.4 mg, 0.09 mmol, 1.8 eq.) followed by sodium triacetoxyborohydride (21 mg, 15 µL, 2 Eq, 0.10 mmol). The mixture was stirred at room temperature for 50 minutes and concentrated. The residue was purified by reverse-phase chromatography (acetonitrile/ 0.05% formic acid) to afford (S)-3-(1'-((2-(2-fluoro-4-((1R,2R)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (13.88 mg, 16.54 µmol, 33 %)(13.88 mg, 33% yield) as white solid. LC-MS purity: 100% (UV at 254 nm),839.6 $[M+H]^+$.

[0751] ^{1}H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 8.32 (s, 1H), 7.45 (s, 1H), 7.16 – 6.96 (m, 5H), 6.78 (d, J = 6.8 Hz, 2H), 6.58 – 6.46 (m, 3H), 6.10 (d, J = 13.6 Hz, 1H), 5.68 (d, J = 8.0 Hz, 1H), 5.07 (dd, J = 13.2, 4.8 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.45 (s, 2H), 4.34 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 16.8 Hz, 1H), 2.93 (s, 3H), 2.83 – 2.78 (m, 2H), 2.70 – 2.54 (m, 2H), 2.48 – 2.24 (m, 2H), 2.21 – 2.06 (m, 4H), 2.00 – 1.85 (m, 8H), 1.73 – 1.59 (m, 6H), 1.54 – 1.34 (m, 4H), 0.95 – 0.87 (m, 2H).

[0752] Compounds A173, A174, A175, and A176 were prepared according to the following reaction schemes



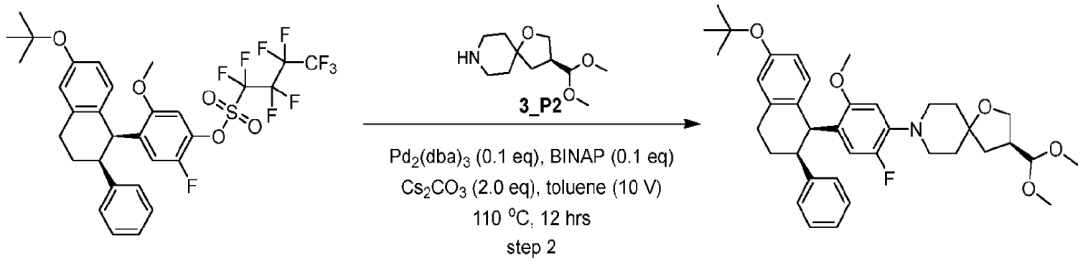
Step 1: Synthesis of 4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



1 2

[0753] To a solution of compound **1** (4.5 g, 10.70 mmol, 1 eq) in MeCN (45 mL) and THF (45 mL) was added K_2CO_3 (2.22 g, 16.05 mmol, 1.5 eq) and 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (4.85 g, 16.05 mmol, 2.82 mL, 1.5 eq) at 20 °C. The mixture was stirred at 20 °C for 12 hours and turned to a light yellow suspension. TLC (Petroleum ether/Ethyl acetate = 10/1, R_f = 0.20) indicated compound **1** was consumed completely and one new spot formed. The reaction mixture was filtered and concentrated under reduced pressure to give the crude product. Compound **2** (8 g, crude) was obtained as a light yellow solid.

Step 2: Synthesis of (S)-8-(4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane

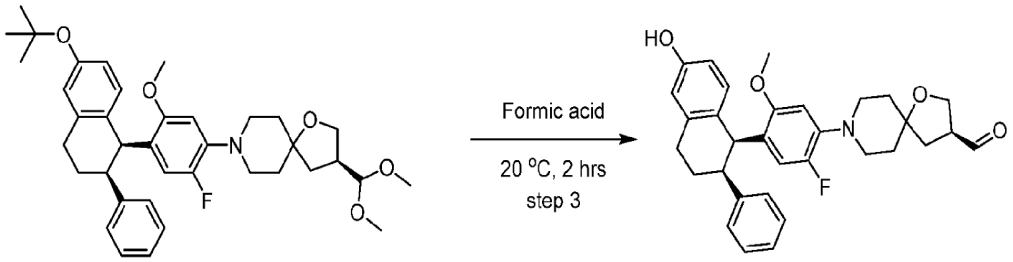


2 4

[0754] To a solution of compound **2** (2 g, 2.85 mmol, 1 eq) in toluene (20 mL) was added compound **3_P2** (919.25 mg, 4.27 mmol, 1.5 eq), $Pd_2(dba)_3$ (260.67 mg, 284.66 umol, 0.1 eq), BINAP (177.25 mg, 284.66 umol, 0.1 eq) and Cs_2CO_3 (1.85 g, 5.69 mmol, 2 eq). Then the mixture was stirred at 110 °C for 12 hrs. TLC (Petroleum ether/Ethyl acetate = 5/1) showed that a little of compound **2** was consumed and the desired product was detected. The mixture was filtered, and the organic layers was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc= 30/1 to 5/1). The

desired product compound **4** (0.8 g, 1.29 mmol, 45.49% yield, 100% purity) was obtained as yellow oil.

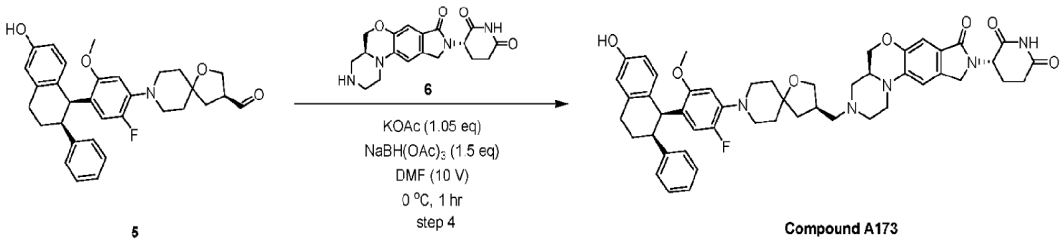
Step 3: Synthesis of (S)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde



4 **5**

[0755] A solution of compound **4** (0.1 g, 161.87 umol, 1 eq) in formic acid (2 mL) was stirred at 20 °C for 1 hr. LCMS showed that compound **4** was consumed and the desired product was detected. The mixture was concentrated under reduced pressure to give a residue. The desired product compound **5** (0.35 g, crude) was obtained as a yellow oil. m/z+1=516.4

*Step 3: Synthesis of (S)-3-((S)-3-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (compound **A173**)*

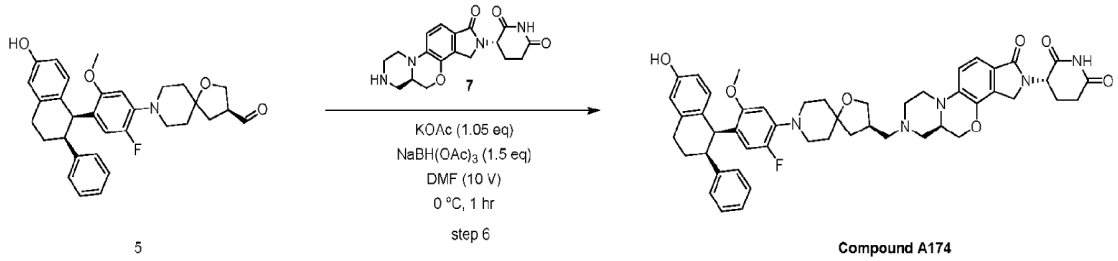


5 **Compound A173**

[0756] To a solution of compound **6** (64.76 mg, 164.85 umol, 1.0 eq, HCl) in DMF (1 mL) was added KOAc (16.99 mg, 173.09 umol, 1.05 eq) to the mixture at 20°C. Then the mixture was cooled to 0°C, and $NaBH(OAc)_3$ (52.41 mg, 247.28 umol, 1.5 eq) was added to the mixture. A solution compound **5** (0.085 g, 164.85 umol, 1 eq) in formic acid (0.3 mL) was added at 0 °C, and then the mixture was stirred at 0 °C for 5 hrs. LCMS showed that compound **5** was consumed and the desired product was detected. The mixture was quenched with water (0.2 mL). The residue was purified by pre-HPLC (column: Phenomenex C18 75*30mm*3um; mobile phase: [water

(FA)-ACN];B%: 35%-60%,8min). The desired product (0.073 g, 84.08 umol, 51.00% yield, 98.59% purity) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d6) 10.93 (br s, 1H), 9.15 (br s, 1H), 7.13 - 7.02 (m, 4H), 6.94 (s, 1H), 6.78 - 6.72 (m, 2H), 6.61 - 6.53 (m, 2H), 6.48 (dd, J=2.3, 8.4 Hz, 1H), 6.24 - 6.14 (m, 2H), 5.03 (dd, J=5.2, 13.3 Hz, 1H), 4.67 (br d, J=5.1 Hz, 1H), 4.32 - 4.22 (m, 2H), 4.19 - 4.11 (m, 1H), 3.95 - 3.86 (m, 2H), 3.82 (br d, J=11.6 Hz, 1H), 3.19 (br d, J=9.1 Hz, 2H), 3.05 - 2.84 (m, 13H), 2.81 - 2.73 (m, 1H), 2.62 - 2.54 (m, 2H), 2.41 - 2.30 (m, 3H), 2.21 - 2.05 (m, 2H), 1.97 (br dd, J=7.9, 11.8 Hz, 2H), 1.77 - 1.57 (m, 6H), 1.37 (br dd, J=8.3, 12.3 Hz, 1H). m/z+1=856.3

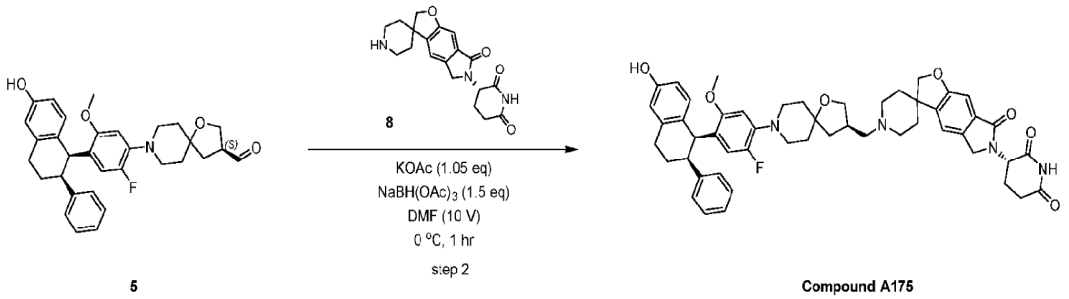
*Step 4: Synthesis of (S)-3-((R)-7-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (compound **A174**)*



[0757] To a solution of compound **7** (64.76 mg, 164.85 umol, 1.0 eq, HCl) in DMF (1 mL) was added KOAc (16.99 mg, 173.09 umol, 1.05 eq) at 20 °C. The mixture was cooled to 0°C, and then $NaBH(OAc)_3$ (52.41 mg, 247.28 umol, 1.5 eq) was added to the mixture. Then a solution of compound **5** (0.085 g, 164.85 umol, 1 eq) in formic acid (0.3 mL) was added to the mixture at 0 °C. The mixture was stirred at 0 °C for 2 hrs. LCMS showed that compound **5** was consumed and the desired product was detected. The mixture was quenched with water (0.5 mL). The mixture was purified by pre-HPLC (column: Phenomenex C18 75*30mm*3um; mobile phase: [water (FA)-ACN];B%: 35%-60%,8min). The desired product (0.083 g, 96.96 umol, 58.82% yield) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d6) 10.94 (br s, 1H), 9.16 (br s, 1H), 7.18 (d, *J*=8.3 Hz, 1H), 7.14 - 6.98 (m, 4H), 6.75 (br d, *J*=6.3 Hz, 2H), 6.63 - 6.54 (m, 2H), 6.52 - 6.44 (m, 1H), 6.28 - 6.14 (m, 2H), 5.03 (dd, *J*=5.0, 13.3 Hz, 1H), 4.67 (br d, *J*=5.1 Hz, 1H), 4.36 (br d, *J*=9.3 Hz, 1H), 4.31 - 4.19 (m, 1H), 4.11 (br d, *J*=16.9 Hz, 1H), 4.01 - 3.78 (m, 3H), 3.19 (br d, *J*=8.5 Hz, 3H), 3.05 - 2.83 (m, 13H), 2.80 - 2.71 (m, 1H), 2.63 - 2.55 (m, 2H), 2.41 - 2.27 (m, 2H),

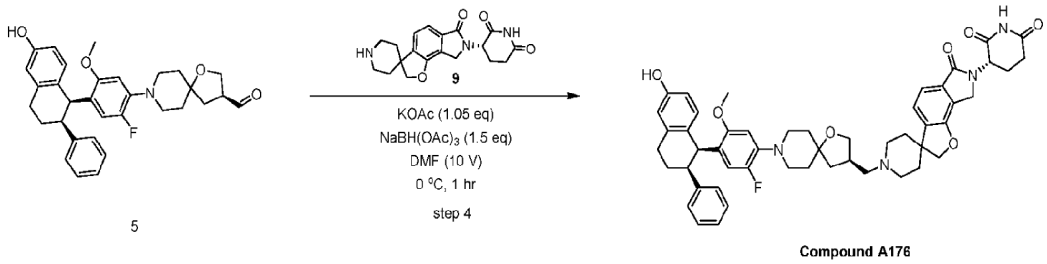
2.13 (br t, *J*=11.3 Hz, 2H), 1.96 (br dd, *J*=7.3, 12.0 Hz, 2H), 1.77 - 1.56 (m, 6H), 1.37 (br dd, *J*=8.3, 12.4 Hz, 1H). m/z+1=856.3

*Step 5: Synthesis of (S)-3-(1'-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (Compound **A175**)*



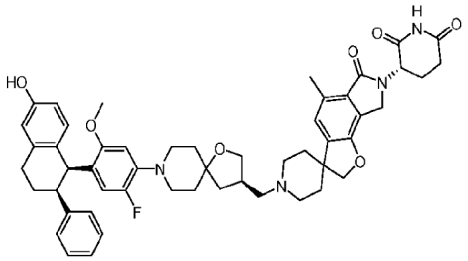
[0758] To a solution of compound **8** (76.00 mg, 193.94 umol, 1.0 eq, HCl) in DMF (2 mL) was added KOAc (19.99 mg, 203.64 umol, 1.05 eq) at 20 °C. The mixture was cooled to 0 °C, and then $NaBH(OAc)_3$ (61.66 mg, 290.92 umol, 1.5 eq) was added to the mixture. Then a solution of compound **5** (0.1 g, 193.94 umol, 1 eq) in formic acid (0.5 mL) was added at 0 °C. The mixture was stirred at 0 °C for 5 hrs. LCMS showed that compound **5** was consumed and the desired product was detected. The mixture was quenched with water (0.2 mL). The mixture was purified by pre-HPLC (column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [water (FA)-ACN];B%: 50%-90%,8min). The desired product (0.057 g, 66.67 umol, 34.37% yield) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d6) 10.97 (br s, 1H), 9.74 - 8.67 (m, 1H), 7.46 (br s, 1H), 7.20 - 6.99 (m, 4H), 6.76 (br d, J=5.8 Hz, 2H), 6.65 - 6.40 (m, 3H), 6.20 (br d, J=10.3 Hz, 2H), 5.08 (br d, J=8.8 Hz, 1H), 4.68 (br s, 1H), 4.46 (br s, 2H), 4.37 - 4.30 (m, 1H), 4.28 - 4.14 (m, 1H), 3.88 (br s, 1H), 3.28 (br s, 1H), 3.05 - 2.78 (m, 12H), 2.59 (br d, J=16.0 Hz, 2H), 2.42 - 2.28 (m, 3H), 2.16 (br d, J=7.3 Hz, 1H), 2.08 - 1.82 (m, 7H), 1.66 (br s, 7H), 1.38 (br d, J=8.4 Hz, 1H). m/z+1=855.3

*Step 6: Synthesis of (S)-3-(1'-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (compound **A176**)*



[0759] To a mixture of compound **9** (64.6 mg, 164.85 umol, 1.0 eq, HCl) in DMF (2 mL) was added KOAc (16.9 mg, 173 umol, 1.05 eq) at 20 °C. The mixture was cooled to 0 °C, and then $NaBH(OAc)_3$ (52.4 mg, 247 umol, 1.5 eq) was added to the mixture. Then a solution of compound **5** (0.085 g, 164 umol, 1 eq) in formic acid (0.6 mL) was added at 0 °C. The mixture was stirred at 0 °C for 5 hrs. LCMS showed that compound **5** was consumed and the desired product was detected. The mixture was quenched with water (0.5 mL). The mixture was purified by pre-HPLC (column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [water (FA)-ACN]; B%: 50%-90%,8min). The desired product (0.053 g, 61.39 umol, 37.24% yield, 99.04% purity) was obtained as a white solid. ^{1}H NMR (400MHz, DMSO-d6) 10.98 (br s, 1H), 9.54 - 8.54 (m, 1H), 7.48 - 7.20 (m, 2H), 7.09 (br s, 3H), 6.76 (br d, *J*=4.0 Hz, 2H), 6.65 - 6.41 (m, 3H), 6.20 (br d, *J*=9.8 Hz, 2H), 5.09 (br d, *J*=8.6 Hz, 1H), 4.68 (br s, 1H), 4.52 (br s, 2H), 4.38 (br d, *J*=17.0 Hz, 1H), 4.22 (br d, *J*=16.8 Hz, 1H), 3.89 (br s, 1H), 3.28 (br s, 1H), 3.02 - 2.78 (m, 13H), 2.59 (br d, *J*=16.5 Hz, 2H), 2.45 - 2.29 (m, 3H), 2.15 (br s, 1H), 1.97 (br d, *J*=11.9 Hz, 6H), 1.67 (br s, 7H), 1.37 (br s, 1H). m/z+1=855.3

Compound A208. (3S)-3-[1'-[[(3R)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione



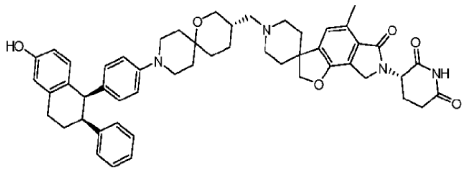
Step 1: Synthesis of (3S)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde

[0760] (S)-8-(4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (50.0 mg, 80.9 μmol, 1.00 eq) was stirred in formic acid (1 mL) at 20 °C for 1 hour and turned yellow solution. The mixture was concentrated under reduced pressure to give the product (0.5 mL solution) at 20 °C. (3S)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde was obtained as a yellow solution. m/e+1=516.3

Step 2: Synthesis of (3S)-3-[1'-[[(3R)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione

[0761] To the suspension of (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (38.1 mg, 84.5 μmol, 1.05 eq, HCl) in DMF (1 mL) was added KOAc (8.29 mg, 84.5 μmol, 1.05 eq) in portions at 20 °C, and stirred for 10 minutes. The mixture was cooled to 0 °C, $NaBH(OAc)_3$ (25.6 mg, 121 μmol, 1.50 eq) and the solution of (3S)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (41.5 mg, 80.5 umol, 1.00 eq) in formic acid (0.5 mL) was added in portions at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour and turned brown solution. The reaction mixture was purified by prep-HPLC (column: Phenomenex Luna C18 200 * 40 mm * 10 um; mobile phase: [water (FA)-ACN]; B%: 25%-60%, 8 min). (3S)-3-[1'-[[(3R)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione (37.6 mg, 43.3 μmol, 53.8% yield, 100% purity) was obtained as a white solid, which was indicated by HNMR. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 9.13 (s, 1H), 7.21 - 7.03 (m, 4H), 6.75 (br d, J = 7.8 Hz, 2H), 6.64 - 6.54 (m, 2H), 6.50 - 6.41 (m, 1H), 6.23 - 6.11 (m, 2H), 5.04 (dd, J = 5.2, 13.0 Hz, 1H), 4.67 (br d, J = 5.3 Hz, 1H), 4.52 - 4.41 (m, 2H), 4.35 - 4.25 (m, 1H), 4.14 (d, J = 17.0 Hz, 1H), 3.88 (br t, J = 7.6 Hz, 1H), 3.45 (br t, J = 7.8 Hz, 1H), 3.24 (br s, 1H), 3.03 - 2.77 (m, 13H), 2.60 (br s, 2H), 2.54 (s, 3H), 2.33 (br s, 2H), 2.15 (br dd, J = 6.9, 12.7 Hz, 1H), 2.03 - 1.82 (m, 7H), 1.64 (br s, 7H). m/e+1=869.4.

Compound A209. (3S)-3-[1'-[[(3S)-9-[4-[(1R,2S)-6-Hydroxy-2-phenyl-tetralin-1-yl]phenyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione



Step 1: Synthesis of (3R)-9-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-1-oxa-9-azaspiro[5.5]undecane-3-carbaldehyde

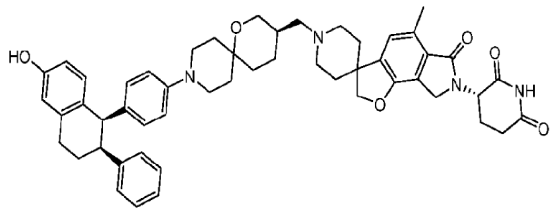
[0762] (R)-9-(4-((1R,2S)-6-(tert-Butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane (40.0 mg, 68.5 μmol, 1.00 eq) was stirred in formic acid (1 mL) at 20 °C for 1 hour and turned yellow solution. The mixture was concentrated under reduced pressure to give the product (0.5 mL solution) at 20 °C. (R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecane-3-carbaldehyde was obtained as a yellow solution. m/e+1=482.4

Step 2: Synthesis of (3S)-3-[1'-[[(3S)-9-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione

[0763] To a suspension of (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (32.4 mg, 71.9 μmol, 1.05 eq, HCl) in DMF (1 mL) was added KOAc (7.06 mg, 71.9 μmol, 1.05 eq) in portions at 20 °C, and stirred for 10 minutes. The mixture was cooled to 0 °C, $NaBH(OAc)_3$ (21.8 mg, 103 μmol, 1.5 eq) and the solution of (R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecane-3-carbaldehyde (33.0 mg, 68.5 μmol, 1.00 eq) in formic acid (0.5 mL) was added in portions at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour and turned brown solution. The reaction mixture was purified by prep-HPLC (column: Phenomenex Luna C18 200 * 40 mm * 10 um; mobile phase: [water (FA)-ACN]; B%: 20%-60%, 8 min). (3S)-3-[1'-[[(3S)-9-[4-[(1R,2S)-6-Hydroxy-2-phenyl-tetralin-1-yl]phenyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione (38.1 mg, 45.6 μmol, 66.5% yield, 100% purity) was obtained as a white solid, which was indicated by HNMR. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1 H), 9.10 (br s, 1 H), 7.02 - 7.22 (m, 4 H), 6.82 (br d, J = 7.13 Hz, 2 H), 6.42 - 6.71 (m, 5 H), 6.14 - 6.26 (m, 2 H), 5.03 (br dd, J = 13.32, 4.94 Hz, 1 H), 4.42 - 4.50 (m, 2 H), 4.24 - 4.33 (m, 1 H), 4.09 - 4.18 (m, 2 H), 3.66 (br dd, J = 10.76, 2.63 Hz, 1 H), 3.10 - 3.16 (m, 2 H), 2.73 - 3.03 (m, 9 H), 2.56 -

2.66 (m, 3 H), 2.37 - 2.44 (m, 1 H), 1.82 - 2.26 (m, 10 H), 1.47 - 1.78 (m, 8 H), 1.28 - 1.46 (m, 3 H). m/c+1=835.4

Compound A210. (3S)-3-[1'-[[(3R)-9-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione



Step 1: Synthesis of (3S)-9-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-1-oxa-9-azaspiro[5.5]undecane-3-carbaldehyde

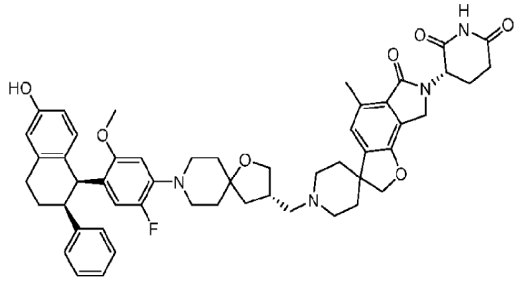
[0764] (S)-9-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane (40.0 mg, 68.5 μmol, 1.00 eq) was stirred in formic acid (1 mL) at 20 °C for 1 hour and turned yellow solution. The mixture was concentrated under reduced pressure to give the product (0.5 mL solution) at 20 °C. (3S)-9-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-1-oxa-9-azaspiro[5.5]undecane-3-carbaldehyde was obtained as a yellow solution. m/e+1=482.4

Step 2: Synthesis of (3S)-3-[1'-[[(3R)-9-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-1-oxa-9-azaspiro[5.5]undecan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione

[0765] To the suspension of (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (32.4 mg, 71.9 μmol, 1.05 eq, HCl) in DMF (1 mL) was added KOAc (7.06 mg, 71.9 μmol, 1.05 eq) in portions at 20 °C, and stirred for 10 minutes. The mixture was cooled to 0 °C, $NaBH(OAc)_3$ (21.8 mg, 103 μmol, 1.50 eq) and the solution of (3S)-9-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-1-oxa-9-azaspiro[5.5]undecane-3-carbaldehyde (33.0 mg, 68.5 μmol, 1.00 eq) in formic acid (0.5 mL) was added in portions at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour and turned brown solution. The reaction mixture was purified by prep-HPLC (column: Phenomenex Luna C18 200 * 40 mm * 10 um; mobile phase: [water (FA)-ACN]; B%: 20%-60%, 8 min). (3S)-3-[1'-[[(3R)-9-[4-[(1R,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]phenyl]-1-oxa-9-azaspiro[5.5]undecan-3-

yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione (21.0 mg, 24.7 μmol, 36.0% yield, 98.1% purity) was obtained as a white solid, which was indicated by HNMR. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 - 11.13 (m, 1 H), 8.97 - 9.31 (m, 1 H), 7.06 - 7.32 (m, 4 H), 6.79 - 6.97 (m, 2 H), 6.44 - 6.69 (m, 5 H), 6.12 - 6.38 (m, 2 H), 4.96 - 5.15 (m, 1 H), 4.41 - 4.57 (m, 2 H), 4.26 - 4.39 (m, 1 H), 4.07 - 4.22 (m, 2 H), 3.66 (br d, *J* = 11.26 Hz, 1 H), 3.15 (br dd, *J* = 4.63, 1.88 Hz, 2 H), 2.72 - 3.07 (m, 9 H), 2.60 - 2.68 (m, 2 H), 2.31 - 2.44 (m, 1 H), 1.86 - 2.30 (m, 10 H), 1.47 - 1.79 (m, 9 H), 1.24 - 1.46 (m, 3 H). m/e+1= 835.4

Compound A211. (3S)-3-[1'-[[(3S)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione



Step 1: Synthesis of (3R)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde

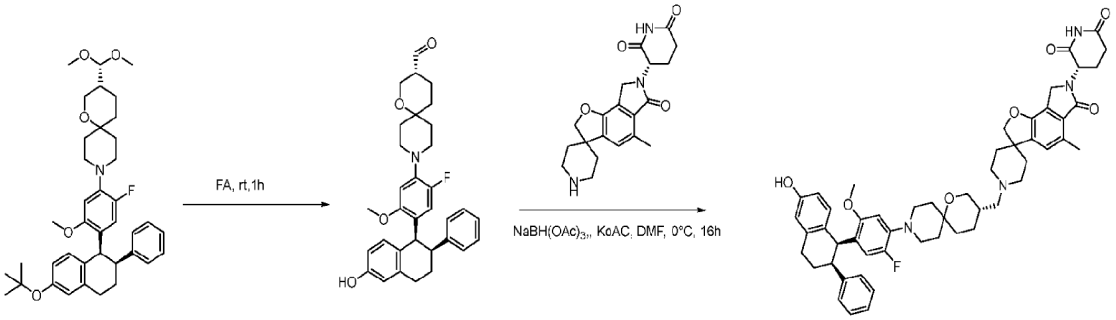
[0766] (R)-8-(4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (50.0 mg, 80.9 μmol, 1.00 eq) was stirred in formic acid (1 mL) at 20 °C for 1 hour and turned yellow solution. The mixture was concentrated under reduced pressure to give the product (0.5 mL solution) at 20 °C. (R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde was obtained as a yellow solution. m/e+1=516.3

Step 2: Synthesis of (3S)-3-[1'-[[(3S)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione

[0767] To the suspension of (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (38.1 mg, 84.5 μmol, 1.05 eq, HCl) in DMF (1 mL) was added KOAc (8.29 mg, 84.5 μmol, 1.05 eq) in portions at 20 °C, and stirred for 10

minutes. The mixture was cooled to 0 °C, $NaBH(OAc)_3$ (25.6 mg, 121 µmol, 1.50 eq) and the solution of (R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (41.5 mg, 80.5 umol, 1.00 eq) in formic acid (0.5 mL) was added in portions at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour and turned brown solution. The reaction mixture was purified by prep-HPLC (column: Phenomenex Luna C18 200 * 40 mm * 10 µm; mobile phase: [water (FA)-ACN]; B%: 25%-60%, 8 min). (3S)-3-[1'-[[(3S)-8-[2-fluoro-4-[(1S,2S)-6-hydroxy-2-phenyl-tetralin-1-yl]-5-methoxy-phenyl]-1-oxa-8-azaspiro[4.5]decan-3-yl]methyl]-5-methyl-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl]piperidine-2,6-dione (35.46 mg, 40.80 µmol, 50.70% yield, 100% purity) was obtained as a white solid, which was indicated by HNMR. ^1H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1 H), 8.98 - 9.26 (m, 1 H), 6.96 - 7.21 (m, 3 H), 6.75 (br d, *J* = 6.32 Hz, 2 H), 6.44 - 6.61 (m, 3 H), 6.13 - 6.25 (m, 2 H), 5.03 (br dd, *J* = 13.35, 5.01 Hz, 1 H), 4.67 (br d, *J* = 5.01 Hz, 1 H), 4.43 - 4.52 (m, 2 H), 4.29 (br d, *J* = 17.17 Hz, 1 H), 4.14 (br d, *J* = 16.93 Hz, 1 H), 3.87 (br t, *J* = 7.81 Hz, 1 H), 3.47 (br s, 1 H), 2.81 - 3.02 (m, 13 H), 2.56 - 2.67 (m, 5 H), 2.38 - 2.43 (m, 1 H), 2.32 (br d, *J* = 6.44 Hz, 2 H), 2.15 (br dd, *J* = 12.58, 6.02 Hz, 1 H), 1.82 - 2.04 (m, 6 H), 1.58 - 1.78 (m, 7 H), 1.31 - 1.39 (m, 1 H). m/e+1= 869.4.

Compound A227 : (S)-3-(1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



Step 1: (R)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecane-3-carbaldehyde

[0768] To a mixture of (S)-9-(4-((1S,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-2-fluoro-5-methoxyphenyl)-3-(dimethoxymethyl)-1-oxa-9-azaspiro[5.5]undecane (20.0 mg,

1.0 Eq, 31.7 μmol) in HCOOH (1.50 mL) was stirred at rt for 1h. The mixture was concentrated to give (S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecane-3-carbaldehyde (20.0 mg) crude as yellow oil.

[0769] LC-MS (ESI, m/z): mass calcd.529.26; found, 530.3 $[M+H]^+$.

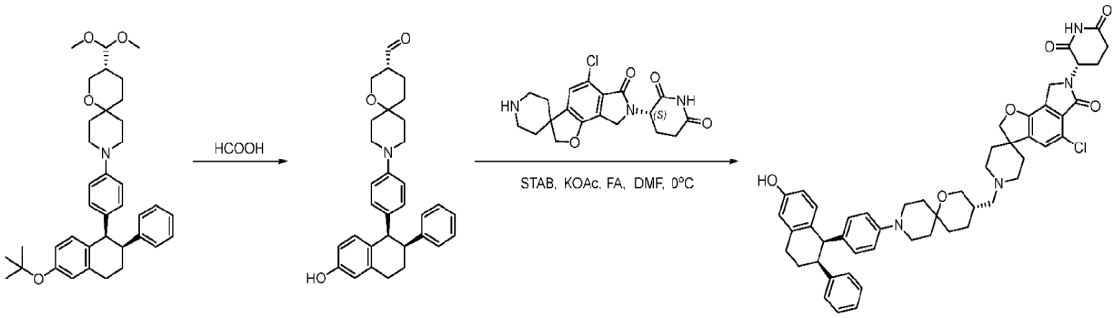
Step 2: (S)-3-(1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

[0770] To a mixture of (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione HCl salt (20 mg, 0.049 mmol, 1.3 eq) in DMF (1.50 mL) was added potassium acetate (3.89 mg, 0.040 mmol, 1.05 eq) at rt, then followed by the addiiotn of Sodium triacetoxyborohydride (12 mg, 0.057 mmol, 1.5 eq) and (S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecane-3-carbaldehyde (20.0 mg, 0.038 mmol, 1.0 eq) in HCOOH (0.30 mL) successively at 0°C. The resulting mixture was stirred at rt for 16 hours, concentrated. The residue was purified by reverse-phase chromatography (0-50%Acetonitrile/ 0.05% Formic acid) to afford (S)-3-(1'-(((R)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (4.57 mg, yield: 13.3 %) as a white solid.

[0771] LC-MS (ESI, m/z): mass calcd. For $C_{53}H_{59}FN_4O_7$, 882.44; found, 883.1 $[M+H]^+$.

[0772] ^1H NMR (400 MHz, DMSO-d6): δ 10.96 (s, 1 H), 9.13 (s, 1 H), 7.06-7.16 (m, 4 H), 6.73-6.79 (m, 2 H), 6.51-6.61 (m, 2 H), 6.47 (dd, J = 8.4 Hz, 2.0 Hz, 1 H), 6.19 (dd, J = 10.0 Hz, 2.0 Hz, 2 H), 5.00-5.08 (m, 1 H), 4.65-4.69 (m, 1 H), 4.43-4.51 (m, 2 H), 4.29 (d, J = 16.8 Hz, 1 H), 4.14 (d, J = 16.8 Hz, 1 H), 3.65-3.72 (m, 1 H), 3.20-3.28 (m, 3 H), 2.74-3.03 (m, 13 H), 2.59-2.63 (m, 1 H), 2.27-2.45 (m, 2 H), 2.05-2.22 (m, 4 H), 1.83-2.03 (m, 5 H), 1.53-1.81 (m, 8 H), 1.43-1.52 (m, 1 H), 1.29-1.41 (m, 2 H).

Compound A231 : (S)-3-(5-chloro-1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

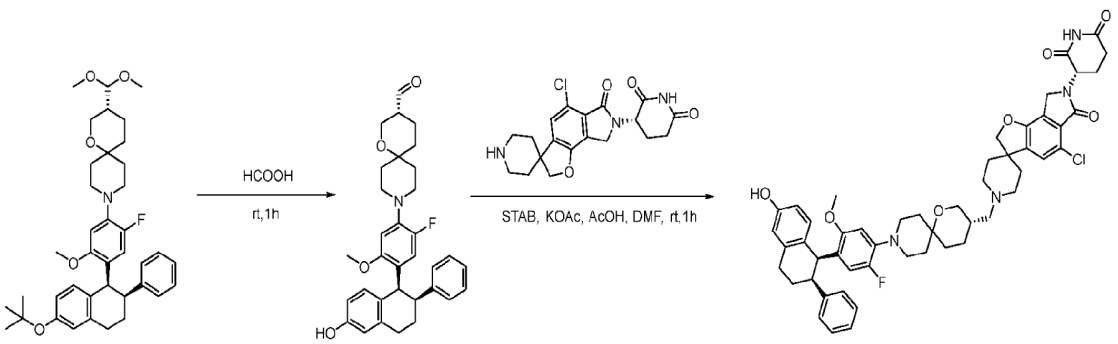


[0773] The synthesis of (S)-3-(5-chloro-1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione was similar to **Compound A227** and finally to give (S)-3-(5-chloro-1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (14.71 mg, 40 %) as a white solid.

[0774] LC-MS (ESI, m/z): mass calcd. For $C_{51}H_{55}ClN_4O_6$, 854.38; found, 855.4 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1 H), 9.11 (s, 1 H), 7.43 (s, 1 H), 7.16-7.11 (m, 3 H), 6.83 (d, J = 6.4 Hz, 2 H), 6.66-6.60 (m, 2 H), 6.54-6.47 (m, 3 H), 6.21 (d, J = 8.4 Hz, 2 H), 5.07-5.03 (m, 1 H), 4.54 (s, 2 H), 4.36-4.16 (m, 2 H), 4.13-4.12 (m, 1 H), 3.68-3.65 (m, 2 H), 3.17 (s, 6 H), 3.01-2.75 (m, 6 H), 2.19-2.13 (m, 2 H), 2.07-1.90 (m, 6 H), 1.72-1.62 (m, 5 H), 1.59-1.52 (m, 3 H), 1.34-1.24 (m, 4 H).

Compound A232: (S)-3-(5-chloro-1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

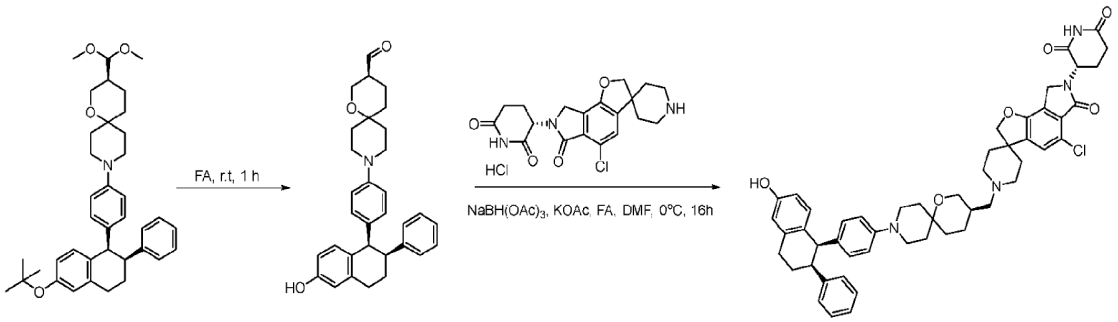


[0775] The synthesis of (S)-3-(5-chloro-1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione was similar to **Compound A227** and finally to give (S)-3-(5-chloro-1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (21.7 mg, 43.0 %) as a white solid.

[0776] LC-MS (ESI, m/z): mass calcd. For $C_{51}H_{55}ClN_4O_6$, 854.4; found, 855.2 $[M+H]^+$.

[0777] ^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1 H), 9.10 (s, 1 H), 7.43 (s, 1 H), 7.20-7.06 (m, 3 H), 6.83 (d, J = 6.4 Hz, 2 H), 6.67-6.58 (m, 2 H), 6.57-6.43 (m, 3 H), 6.20 (d, J = 8.4 Hz, 2 H), 5.05 (dd, J = 13.2, 5.2 Hz, 1 H), 4.59-4.48 (m, 2 H), 4.37-4.28 (m, 1 H), 4.23-4.10 (m, 2 H), 3.70-3.63 (m, 1 H), 3.17-3.10 (m, 2 H), 3.03-2.74 (m, 8 H), 2.63-2.55 (m, 2 H), 2.43-2.34 (m, 1 H), 2.22-2.08 (m, 3 H), 2.04-1.86 (m, 6 H), 1.76-1.52 (m, 8 H), 1.44-1.28 (m, 3 H).

Compound A233: (S)-3-(5-chloro-1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

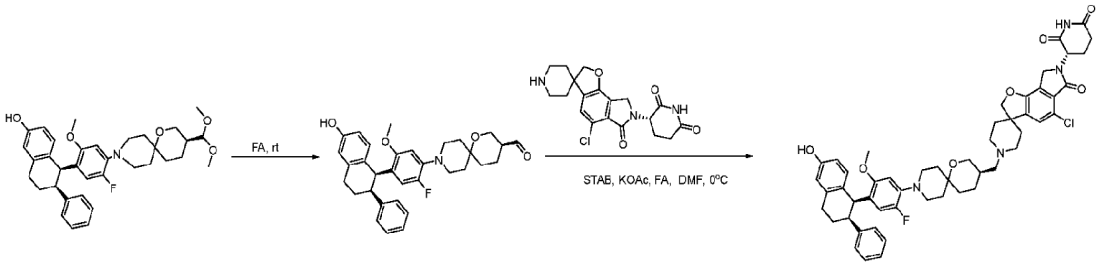


[0778] The synthesis of (S)-3-(5-chloro-1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione was similar to **Compound A227** and finally to give (S)-3-(5-chloro-1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (28.42 mg, 37.9 %) as a white solid.

[0779] LC-MS (ESI, m/z): mass calcd. For $C_{51}H_{55}ClN_4O_6$, 854.38; found, 855.2 $[M+H]^+$.

[0780] ^{1}H NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1 H), 9.09 (s, 1 H), 7.43 (s, 1 H), 7.08-7.18 (m, 3 H), 6.79-6.86 (m, 2 H), 6.65 (d, J = 8.8 Hz, 1 H), 6.60 (d, J = 2.4 Hz, 1 H), 6.53 (d, J = 8.8 Hz, 2 H), 6.48 (dd, J = 8.4 Hz, 2.4 Hz, 1 H), 6.20 (d, J = 8.8 Hz, 2 H), 5.01-5.09 (m, 1 H), 4.50-4.58 (m, 2 H), 4.34 (d, J = 17.6 Hz, 1 H), 4.17 (d, J = 17.2 Hz, 1 H), 4.12 (d, J = 5.2 Hz, 1 H), 3.36-3.71 (m, 1 H), 3.20-3.27 (m, 1 H), 3.09-3.19 (m, 2 H), 2.83-3.03 (m, 5 H), 2.73-2.83 (m, 2 H), 2.55-2.62 (m, 2 H), 2.31-2.44 (m, 2 H), 1.86-2.24 (m, 9 H), 1.28-1.78 (m, 10 H).

Compound A234: (S)-3-(5-chloro-1'-(((R)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

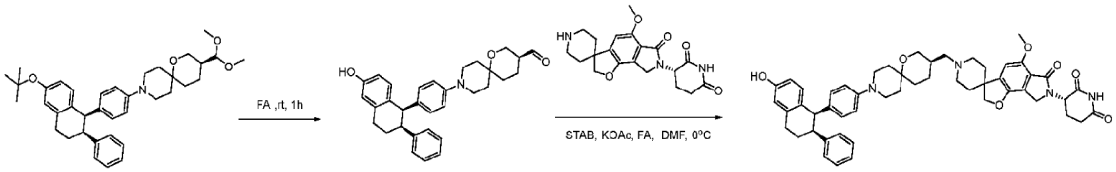


[0781] The synthesis of (S)-3-(5-chloro-1'-(((R)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione was similar to **Compound A227** and finally to give (S)-3-(5-chloro-1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (9.54 mg, 25.3 %) as a white solid.

[0782] LC-MS (ESI, m/z): mass calcd. For $C_{52}H_{56}ClFN_4O_7$, 902.38; found, 903.2 $[M+H]^+$.

[0783] ^{1}H NMR (400 MHz, DMSO-d6): δ 10.98 (s, 1 H), 8.19 (s, 1 H), 7.46-7.37 (m, 1 H), 7.14-7.03 (m, 3 H), 6.80-6.62 (m, 2 H), 6.62-6.52 (m, 2 H), 6.51-6.45 (m, 1 H), 6.27-6.15 (m, 2 H), 5.05 (dd, J = 13.2 Hz, 5.2 Hz, 1 H), 4.67 (d, J = 5.2 Hz, 1 H), 4.58-4.49 (m, 2 H), 4.40-4.30 (m, 1 H), 4.25-4.15 (m, 1 H), 3.71-3.66 (m, 1 H), 3.28-3.23 (m, 2 H), 3.02-2.83 (m, 11 H), 2.81-2.72 (m, 2 H), 2.64-2.57 (m, 1 H), 2.45-2.36 (m, 1 H), 2.22-2.10 (m, 3 H), 2.01-1.87 (m, 5 H), 1.77-1.55 (m, 8 H), 1.50-1.29 (m, 3 H).

Compound A235: (S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

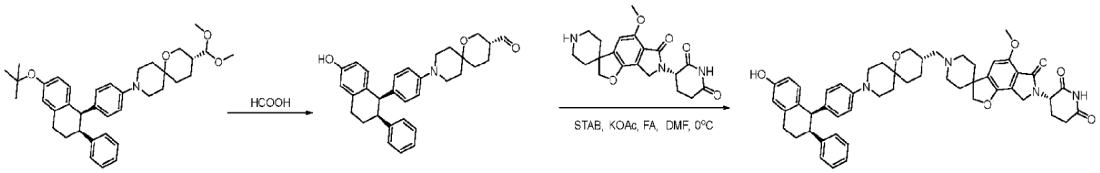


[0784] The synthesis of (S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione was similar to **Compound A227** and finally to give (S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (17.43 mg, 49.8 %) as a white solid.

[0785] LC-MS (ESI, m/z): mass calcd. For $C_{52}H_{58}N_4O_7$, 850.43; found, 851.7 $[M+H]^+$.

[0786] ^{1}H NMR (400 MHz, DMSO-d6): δ 10.92 (s, 1 H), 8.31 (s, 1 H), 7.19-7.08 (m, 3 H), 7.01 (s, 1 H), 6.83 (d, J = 6.8 Hz, 2 H), 6.68-6.59 (m, 2 H), 6.56-6.43 (m, 3 H), 6.20 (d, J = 8.4 Hz, 2 H), 4.99 (dd, J = 13.2 Hz, 4.8 Hz, 1 H), 4.52-4.40 (m, 2 H), 4.31-4.20 (m, 1 H), 4.15-4.06 (m, 2 H), 3.82 (s, 3 H), 3.69-3.65 (m, 1 H), 3.31-3.22 (m, 3 H), 3.16-3.10 (m, 2 H), 2.97-2.83 (m, 5 H), 2.81-2.71 (m, 2 H), 2.64-2.55 (m, 1 H), 2.40-2.31 (m, 1 H), 2.20-2.12 (m, 2 H), 2.04-1.87 (m, 6 H), 1.75-1.50 (m, 8 H), 1.45-1.37 (m, 1 H), 1.37-1.24 (m, 2 H).

Compound A236: (S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0787] The synthesis of (S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-

tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-c]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione was similar to **Compound A227** and finally to give (S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-c]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (20.81 mg, 58.9 %) as a white solid.

[0788] LC-MS (ESI, m/z): mass calcd. For $C_{52}H_{58}N_4O_7$, 850.43; found, 851.7 $[M+H]^+$.

[0789] ^{1}H NMR (400 MHz, DMSO-d6): δ 10.92 (s, 1 H), 8.25 (s, 1 H), 7.18-7.08 (m, 3 H), 7.01 (s, 1 H), 6.83 (d, J = 6.8 Hz, 2 H), 6.73-6.58 (m, 2 H), 6.56-6.43 (m, 3 H), 6.20 (d, J = 8.4 Hz, 2 H), 4.99 (dd, J = 13.2 Hz, 5.2 Hz, 1 H), 4.50-4.38 (m, 2 H), 4.32-4.23 (m, 1 H), 4.14-4.07 (m, 2 H), 3.82 (s, 3 H), 3.66-3.65 (m, 1 H), 3.30-3.21 (m, 3 H), 3.17-3.11 (m, 2 H), 2.98-2.83 (m, 5 H), 2.80-2.73 (m, 2 H), 2.62-2.54 (m, 1 H), 2.39-2.31 (m, 1 H), 2.20-2.13 (m, 2 H), 2.05-1.87 (m, 6 H), 1.77-1.51 (m, 8 H), 1.45-1.38 (m, 1 H), 1.36-1.26 (m, 2 H).

[0790] The rest of examples were prepared in a manner analogous to **Compound A208** by reductive amination using same Method.

[0791] The following examples were prepared in a manner analogous to compound **A8** or **A208** by reductive amination.

Table 4. Characterization Data for "A" Compounds

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
A1	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.87 (s, 1H), 8.61 (d, J = 8.2 Hz, 1H), 8.21 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.17 – 7.09 (m, 3H), 6.83 (d, J = 6.6 Hz, 2H), 6.66 – 6.58 (m, 2H), 6.55 – 6.45 (m, 3H), 6.20 (d, J = 8.6 Hz, 2H), 4.78 – 4.68 (m, 1H), 4.12 (d, J = 4.8 Hz, 1H), 4.01 (s, 3H), 3.53 – 3.23 (m, 6H), 3.10 (s, 4H), 2.97 – 2.75 (m, 4H), 2.57 – 2.52 (m, 2H), 2.27 – 1.98 (m, 6H), 1.78 – 1.61 (m, 4H), 1.21 – 1.09 (m, 2H)	781.4	781.4	F
A2	^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.20 – 7.06 (m, 3H), 6.83 (d, J = 6.4 Hz, 2H), 6.69 – 6.44 (m, 5H), 6.20 (d, J = 8.4 Hz, 2H), 4.76 – 4.66 (m,	741.4	741.4	F

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	1H), 4.47 – 4.39 (m, 1H), 4.16 – 4.02 (m, 2H), 3.77 (d, J = 11.2 Hz, 1H), 3.56 – 3.18 (m, 8H), 3.02 – 2.88 (m, 4H), 2.82 – 2.70 (m, 2H), 2.22 – 1.94 (m, 6H), 1.81 – 1.61 (m, 5H), 1.24 – 1.08 (m, 2H).			
A3	^{1}H NMR (400 MHz, DMSO) δ 10.86 (s, 1H), 9.01 (d, J = 8.4 Hz, 1H), 8.57 (d, J = 1.8 Hz, 1H), 8.27 (s, 1H), 7.98 (d, J = 8.2 Hz, 1H), 7.93 – 7.84 (m, 1H), 7.19 – 7.06 (m, 3H), 6.83 (d, J = 6.6 Hz, 2H), 6.67 – 6.44 (m, 5H), 6.20 (d, J = 8.6 Hz, 2H), 4.83 – 4.72 (m, 1H), 4.13 (d, J = 5.0 Hz, 1H), 3.51 (d, J = 9.8 Hz, 2H), 3.30 – 3.27 (m, 2H), 3.03 – 2.88 (m, 4H), 2.85 – 2.75 (m, 1H), 2.70 – 2.63 (m, 1H), 2.57 – 2.52 (m, 1H), 2.48 – 2.44 (m, 1H), 2.26 – 2.07 (m, 4H), 1.99 (t, J = 10.2 Hz, 3H), 1.82 – 1.55 (m, 8H), 1.21 – 1.07 (m, 2H).	712.4	712.4	F
A4	^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.20 – 7.07 (m, 3H), 6.83 (d, J = 6.6 Hz, 2H), 6.66 – 6.44 (m, 5H), 6.20 (d, J = 8.6 Hz, 2H), 4.75 – 4.67 (m, 1H), 4.48 – 4.38 (m, 1H), 4.16 – 4.03 (m, 2H), 3.77 (d, J = 12.0 Hz, 1H), 3.51 (d, J = 9.6 Hz, 2H), 3.31 – 3.24 (m, 2H), 3.23 – 3.15 (m, 2H), 3.01 – 2.87 (m, 4H), 2.83 – 2.70 (m, 2H), 2.56 – 2.52 (m, 1H), 2.48 – 2.44 (m, 1H), 2.25 – 2.04 (m, 5H), 2.02 – 1.93 (m, 1H), 1.81 – 1.58 (m, 5H), 1.22 – 1.07 (m, 2H).	741.4	741.3	E
A5	^{1}H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 8.86 (d, J = 8.4 Hz, 1H), 8.31 (s, 1H), 8.06 (s, 1H), 7.58 (s, 1H), 7.21 – 7.05 (m, 3H), 6.83 (d, J = 6.6 Hz, 2H), 6.68 – 6.44 (m, 5H), 6.20 (d, J = 8.6 Hz, 2H), 4.81 – 4.69 (m, 1H), 4.12 (d, J = 5.0 Hz, 1H), 3.93 (s, 3H), 3.51 (d, J = 12.4 Hz, 4H), 3.32 – 3.24 (m, 2H), 3.12 (s, 4H), 3.06 – 2.86 (m, 3H), 2.85 – 2.74 (m, 1H), 2.60 – 2.53 (m, 1H), 2.47 – 2.41 (m, 1H), 2.36 – 1.93 (m, 6H), 1.80 – 1.54 (m, 4H), 1.23 – 1.07 (m, 2H).	743.9	743.9	E

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
A6	^{1}H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.50 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.24 – 7.06 (m, 3H), 6.83 (d, J = 6.4 Hz, 2H), 6.72 – 6.57 (m, 2H), 6.56 – 6.40 (m, 3H), 6.21 (d, J = 8.6 Hz, 2H), 4.79 – 4.65 (m, 1H), 4.51 – 4.40 (m, 1H), 4.20 – 4.03 (m, 2H), 3.77 (d, J = 11.4 Hz, 2H), 3.35 – 3.12 (m, 5H), 3.05 – 2.80 (m, 5H), 2.80 – 2.66 (m, 2H), 2.48 – 2.36 (m, 1H), 2.24 – 2.03 (m, 5H), 2.03 – 1.94 (m, 1H), 1.81 – 1.59 (m, 5H), 1.25 – 1.07 (m, 2H).	741.9	741.9	C
A7	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.37 (s, 1H), 7.17 – 7.08 (m, 3H), 7.00 (t, *J* = 8.1 Hz, 2H), 6.79 (dd, *J* = 19.5, 7.5 Hz, 2H), 6.65 – 6.55 (m, 2H), 6.47 (d, *J* = 10.1 Hz, 1H), 6.30 (d, *J* = 8.2 Hz, 1H), 6.17 (d, *J* = 8.4 Hz, 1H), 6.05 (d, *J* = 8.4 Hz, 1H), 5.03 (dd, *J* = 12.9, 4.9 Hz, 1H), 4.35 (d, *J* = 9.9 Hz, 1H), 4.26 (d, *J* = 16.7 Hz, 1H), 4.15 – 4.05 (m, 2H), 4.00 – 3.92 (m, 1H), 3.91 – 3.78 (m, 3H), 3.72 (d, *J* = 7.1 Hz, 1H), 3.69 – 3.59 (m, 2H), 3.57 – 3.47 (m, 3H), 3.21 – 3.14 (m, 2H), 3.06 – 2.87 (m, 5H), 2.76 (dd, *J* = 32.0, 8.0 Hz, 2H), 2.69 – 2.58 (m, 2H), 2.39 – 2.24 (m, 4H), 2.19 – 2.04 (m, 2H), 1.98 – 1.86 (m, 2H), 1.75 – 1.68 (m, 1H).	780.9	780.9	C
A8	^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.12 (s, 1H), 7.19 – 7.07 (m, 4H), 7.04 – 6.95 (m, 2H), 6.80 (dd, J = 16.7, 7.5 Hz, 2H), 6.66 – 6.57 (m, 2H), 6.47 (dd, J = 8.3, 2.6 Hz, 1H), 6.31 (d, J = 8.3 Hz, 1H), 6.18 (d, J = 8.4 Hz, 1H), 6.06 (d, J = 8.3 Hz, 1H), 5.03 (dd, J = 13.1, 4.9 Hz, 1H), 4.31 (d, J = 9.6 Hz, 1H), 4.21 (d, J = 22.7 Hz, 2H), 4.15 – 4.10 (m, 1H), 4.00 – 3.87 (m, 3H), 3.87 – 3.71 (m, 3H), 3.70 – 3.60 (m, 2H), 3.59 – 3.49 (m, 3H), 3.03 – 2.76 (m, 6H), 2.71 – 2.58 (m, 3H), 2.44 – 2.29 (m, 3H), 2.09 (dd, J = 14.0, 8.4 Hz, 1H), 2.01 – 1.82 (m, 3H), 1.69 (d, J = 11.3 Hz, 1H).	780.9	780.9	C

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
A9	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.34 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.09 – 6.94 (m, 4H), 6.78 – 6.68 (m, 2H), 6.59 – 6.49 (m, 2H), 6.46 – 6.41 (m, 1H), 6.39 – 6.25 (m, 2H), 6.10 (s, 1H), 5.12 – 4.96 (m, 1H), 4.64 (d, J = 5.0 Hz, 1H), 4.43 – 4.23 (m, 2H), 4.15 – 4.05 (m, 1H), 4.00 – 3.90 (m, 1H), 3.80 (d, J = 11.2 Hz, 1H), 3.25 – 3.10 (m, 3H), 3.00 (s, 2H), 2.94 – 2.82 (m, 10H), 2.72 (t, J = 10.6 Hz, 1H), 2.55 (s, 1H), 2.48 – 2.34 (m, 4H), 2.22 – 2.05 (m, 2H), 2.01 – 1.91 (m, 3H), 1.73 (t, J = 10.2 Hz, 1H), 1.68 – 1.50 (m, 5H), 1.44 – 1.34 (m, 2H).	823.0	823.1	E
A10	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.28 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.11 – 6.94 (m, 4H), 6.76 – 6.67 (m, 2H), 6.59 – 6.51 (m, 2H), 6.48 – 6.40 (m, 1H), 6.39 – 6.23 (m, 2H), 6.10 (s, 1H), 5.08 – 4.94 (m, 1H), 4.64 (d, J = 5.2 Hz, 1H), 4.37 – 4.19 (m, 2H), 4.16 – 4.04 (m, 1H), 4.02 – 3.92 (m, 1H), 3.85 – 3.78 (m, 1H), 3.27 – 3.11 (m, 3H), 3.00 (s, 2H), 2.95 – 2.82 (m, 11H), 2.76 – 2.65 (m, 1H), 2.63 – 2.54 (m, 1H), 2.48 – 2.34 (m, 4H), 2.21 – 2.06 (m, 2H), 2.01 – 1.88 (m, 3H), 1.82 – 1.69 (m, 1H), 1.67 – 1.50 (m, 5H), 1.46 – 1.36 (m, 2H).	823.0	823.1	C
A11	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.23 (s, 1H), 7.05 (t, J = 7.8 Hz, 4H), 6.93 (s, 1H), 6.72 (d, J = 5.8 Hz, 2H), 6.55 (d, J = 10.8 Hz, 2H), 6.48 – 6.41 (m, 1H), 6.38 – 6.25 (m, 2H), 6.10 (s, 1H), 5.11 – 4.94 (m, 1H), 4.64 (d, J = 5.0 Hz, 1H), 4.28 – 4.10 (m, 3H), 3.94 – 3.76 (m, 3H), 3.26 – 3.10 (m, 3H), 3.00 (s, 2H), 2.96 – 2.85 (m, 10H), 2.79 – 2.72 (m, 1H), 2.62 – 2.54 (m, 1H), 2.45 – 2.36 (m, 3H), 2.24 – 2.08 (m, 2H), 1.98 – 1.88 (m, 3H), 1.76 – 1.66 (m, 1H), 1.65 – 1.44 (m, 5H), 1.47 – 1.36 (m, 2H).	823.0	823.1	C

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
A12	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.32 (s, 2H), 7.09 – 6.98 (m, 4H), 6.93 (s, 1H), 6.77 – 6.67 (m, 2H), 6.61 – 6.50 (m, 2H), 6.47 – 6.40 (m, 1H), 6.36 – 6.21 (m, 2H), 6.10 (s, 1H), 5.09 – 4.97 (m, 1H), 4.64 (d, J = 5.0 Hz, 1H), 4.32 – 4.09 (m, 4H), 3.94 – 3.74 (m, 3H), 3.24 – 3.12 (m, 2H), 3.00 (s, 2H), 2.94 – 2.82 (m, 10H), 2.78 – 2.67 (m, 1H), 2.63 – 2.52 (m, 2H), 2.45 – 2.33 (m, 3H), 2.20 – 2.06 (m, 2H), 1.95 (d, J = 5.2 Hz, 3H), 1.66 – 1.51 (m, 5H), 1.46 – 1.36 (m, 2H).	823.0	823.1	C
A13	^{1}H NMR (400 MHz, DMSO) δ 10.82 (s, 1H), 8.49 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.19 – 7.05 (m, 3H), 6.82 (d, J = 6.8 Hz, 2H), 6.67 – 6.44 (m, 5H), 6.20 (d, J = 8.0 Hz, 2H), 4.76 – 4.66 (m, 1H), 4.43 (d, J = 10.8 Hz, 1H), 4.15 – 4.02 (m, 2H), 3.87 (t, J = 7.4 Hz, 1H), 3.77 (d, J = 11.2 Hz, 1H), 3.44 – 3.43 (m, 1H), 3.30 – 3.26 (m, 1H), 3.22 – 3.17 (m, 1H), 3.08 – 2.88 (m, 9H), 2.82 – 2.72 (m, 2H), 2.65 – 2.54 (m, 2H), 2.35 (d, J = 6.4 Hz, 2H), 2.17 – 1.91 (m, 5H), 1.77 – 1.53 (m, 6H), 1.38 – 1.28 (m, 1H).	797.9	797.8	F
A14	^{1}H NMR (400 MHz, DMSO) δ 10.82 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.18 – 7.06 (m, 3H), 6.82 (d, J = 6.6 Hz, 2H), 6.67 – 6.57 (m, 2H), 6.56 – 6.45 (m, 3H), 6.20 (d, J = 8.6 Hz, 2H), 4.76 – 4.66 (m, 1H), 4.47 – 4.39 (m, 1H), 4.14 – 4.02 (m, 2H), 3.87 (t, J = 7.8 Hz, 1H), 3.76 (d, J = 11.6 Hz, 1H), 3.43 – 3.42 (m, 1H), 3.30 – 3.27 (m, 1H), 3.21 – 3.16 (m, 1H), 3.08 – 2.90 (m, 9H), 2.82 – 2.71 (m, 2H), 2.61 – 2.53 (m, 2H), 2.41 – 2.30 (m, 2H), 2.20 – 2.05 (m, 3H), 2.03 – 1.88 (m, 2H), 1.73 – 1.55 (m, 6H), 1.37 – 1.27 (m, 1H).	797.9	797.8	F

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
A15	^{1}H NMR (400 MHz, DMSO) δ 10.80 (s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.18 – 7.07 (m, 3H), 6.82 (d, J = 6.6 Hz, 2H), 6.66 – 6.44 (m, 5H), 6.20 (d, J = 8.6 Hz, 2H), 4.76 – 4.66 (m, 1H), 4.46 – 4.39 (m, 1H), 4.16 – 4.02 (m, 2H), 3.87 (t, J = 7.8 Hz, 1H), 3.77 (d, J = 11.6 Hz, 1H), 3.45 – 3.43 (m, 1H), 3.27 – 3.21 (m, 2H), 3.10 – 2.85 (m, 9H), 2.81 – 2.71 (m, 2H), 2.68 – 2.52 (m, 2H), 2.39 – 2.30 (m, 2H), 2.19 – 2.03 (m, 3H), 2.01 – 1.87 (m, 2H), 1.75 – 1.52 (m, 6H), 1.37 – 1.28 (m, 1H).	797.9	797.8	E
A16	^{1}H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.17 – 7.08 (m, 3H), 6.82 (d, J = 6.6 Hz, 2H), 6.67 – 6.57 (m, 2H), 6.57 – 6.45 (m, 3H), 6.20 (d, J = 8.6 Hz, 2H), 4.75 – 4.66 (m, 1H), 4.48 – 4.38 (m, 1H), 4.15 – 4.01 (m, 2H), 3.87 (t, J = 7.8 Hz, 1H), 3.77 (d, J = 11.4 Hz, 1H), 3.46 – 3.44 (m, 1H), 3.24 – 3.15 (m, 2H), 3.09 – 2.89 (m, 9H), 2.81 – 2.71 (m, 2H), 2.62 – 2.52 (m, 2H), 2.40 – 2.29 (m, 2H), 2.20 – 2.03 (m, 3H), 2.02 – 1.87 (m, 2H), 1.74 – 1.54 (m, 6H), 1.37 – 1.28 (m, 1H).	797.9	797.8	E
A17	^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.26 (s, 1H), 7.18 – 7.07 (m, 3H), 7.04 (s, 1H), 6.92 (s, 1H), 6.82 (d, J = 6.6 Hz, 2H), 6.67 – 6.44 (m, 5H), 6.20 (d, J = 8.6 Hz, 2H), 5.06-4.99 (m, 1H), 4.31 – 4.23 (m, 2H), 4.17 – 4.08 (m, 2H), 3.93 – 3.81 (m, 3H), 3.43 (t, J = 7.8 Hz,1H), 3.31 – 3.23 (m, 1H), 3.19 – 3.11 (m, 1H), 3.07 – 2.85 (m, 9H), 2.78 – 2.70 (m, 1H), 2.62 – 2.53 (m, 2H), 2.40 – 2.29 (m, 3H), 2.14 – 2.03 (m, 2H), 1.98 – 1.87 (m, 2H), 1.78 – 1.53 (m, 6H), 1.33 (m, 1H).	808.9	808.8	F
A18	^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.30 (s, 1H), 7.18 – 7.07 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.82 (d, J = 6.6 Hz, 2H), 6.68 – 6.44 (m, 5H), 6.20 (d, J = 8.6 Hz, 2H), 5.06-4.99 (m, 1H), 4.31 – 4.23 (m, 2H), 4.17 – 4.09 (m, 2H), 3.93 – 3.79 (m, 3H), 3.44 (t, J	808.9	808.8	F

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	= 7.8 Hz, 1H), 3.31 – 3.23 (m, 1H), 3.18 – 3.10 (m, 1H), 3.07 – 2.87 (m, 9H), 2.79 – 2.70 (m, 1H), 2.61 – 2.53 (m, 2H), 2.41 – 2.27 (m, 3H), 2.17 – 2.04 (m, 2H), 1.98 – 1.88 (m, 2H), 1.74 – 1.52 (m, 6H), 1.36 – 1.28 (m, 1H).			
A19	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.35 (s, 1H), 7.18 – 7.07 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.82 (d, J = 6.6 Hz, 2H), 6.67 – 6.44 (m, 5H), 6.19 (d, J = 8.6 Hz, 2H), 5.06-4.99 (m, 1H), 4.31 – 4.22 (m, 2H), 4.17 – 4.08 (m, 2H), 3.94 – 3.77 (m, 3H), 3.43 (t, J = 8.0 Hz,1H), 3.30 – 3.25 (m, 1H), 3.17 – 3.12 (m, 1H), 3.07 – 2.85 (m, 9H), 2.79 – 2.69 (m, 1H), 2.62 – 2.53 (m, 2H), 2.40 – 2.29 (m, 3H), 2.15 – 2.03 (m, 2H), 1.98 – 1.88 (m, 2H), 1.78 – 1.50 (m, 6H), 1.37 – 1.28 (m, 1H).	808.9	808.8	E
A20	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.33 (s, 1H), 7.18 – 7.07 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.82 (d, J = 6.6 Hz, 2H), 6.67 – 6.45 (m, 5H), 6.19 (d, J = 8.6 Hz, 2H), 5.06-4.99 (m, 1H), 4.32 – 4.22 (m, 2H), 4.16 – 4.08 (m, 2H), 3.94 – 3.78 (m, 3H), 3.43 (t, J = 8.0 Hz, 1H), 3.31 – 3.24 (m, 1H), 3.18 – 3.11 (m, 1H), 3.06 – 2.86 (m, 9H), 2.79 – 2.71 (m, 1H), 2.62 – 2.53 (m, 2H), 2.40 – 2.28 (m, 3H), 2.16 – 2.03 (m, 2H), 1.98 – 1.88 (m, 2H), 1.75 – 1.51 (m, 6H), 1.37 – 1.28 (m, 1H).	808.9	808.8	E
A21	^{1}H NMR (400 MHz, MeOD) δ 7.15 (s, 1H), 7.07 (dd, J = 7.4, 4.0 Hz, 4H), 6.80 – 6.73 (m, 2H), 6.67 – 6.61 (m, 2H), 6.57 (d, J = 8.3 Hz, 1H), 6.51 (dd, J = 8.3, 2.6 Hz, 2H), 6.28 (s, 1H), 5.51 (s, 1H), 5.10 (dd, J = 13.3, 5.2 Hz, 1H), 4.81 (d, J = 5.3 Hz, 1H), 4.41 – 4.27 (m, 3H), 4.03 (dd, J = 11.0, 7.9 Hz, 2H), 3.62 (d, J = 9.2 Hz, 2H), 3.46 (dd, J = 17.5, 12.1 Hz, 2H), 3.26 (d, J = 7.3 Hz, 2H), 3.05 (s, 4H), 2.94 (ddd, J = 18.3, 15.7, 5.4 Hz, 3H), 2.80 (dd, J = 11.9, 7.6 Hz, 3H), 2.68 (s, 2H), 2.53 – 2.41 (m, 1H), 2.38 – 2.25 (m, 2H), 2.16 (dd, J = 11.2, 6.2 Hz, 1H), 1.95 (t, J = 10.1 Hz, 3H),	782.9	782.8	C

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	1.68 (dd, J = 15.3, 5.5 Hz, 1H), 1.52 – 1.42 (m, 2H).			
A22	^{1}H NMR (400 MHz, MeOD) δ 8.29 (s, 1H), 7.29 (s, 1H), 7.12 – 6.87 (m, 4H), 6.74 – 6.66 (m, 2H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.54 (dd, *J* = 9.7, 5.5 Hz, 3H), 6.42 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.21 (d, *J* = 8.6 Hz, 2H), 5.02 (dd, *J* = 13.3, 5.1 Hz, 2H), 4.45 (s, 2H), 4.31 (q, *J* = 16.8 Hz, 2H), 4.08 (d, *J* = 5.0 Hz, 1H), 4.02 – 3.92 (m, 1H), 3.52 – 3.44 (m, 1H), 3.00 (dd, *J* = 12.0, 6.4 Hz, 4H), 2.96 – 2.78 (m, 3H), 2.77 – 2.59 (m, 4H), 2.56 – 2.31 (m, 3H), 2.07 (ddd, *J* = 23.2, 14.8, 7.1 Hz, 5H), 1.82 (d, *J* = 13.5 Hz, 2H), 1.64 (ddd, *J* = 24.5, 12.9, 7.0 Hz, 5H), 1.40 (dd, *J* = 12.4, 8.3 Hz, 1H), 1.19 (s, 2H).	808.0	808.0	C
A23	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.06 (t, J = 5.9 Hz, 3H), 7.01 (d, J = 8.5 Hz, 1H), 6.76 – 6.70 (m, 2H), 6.55 (d, J = 8.8 Hz, 2H), 6.45 (dd, J = 8.3, 2.3 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 6.30 (d, J = 8.7 Hz, 1H), 6.11 (s, 1H), 5.03 (dd, J = 13.3, 5.0 Hz, 1H), 4.64 (d, J = 5.1 Hz, 1H), 4.40 – 4.33 (m, 1H), 4.26 (d, J = 16.9 Hz, 1H), 4.10 (d, J = 16.9 Hz, 1H), 4.00 – 3.92 (m, 1H), 3.83 (d, J = 11.4 Hz, 1H), 3.56 (s, 2H), 3.19 (t, J = 10.8 Hz, 2H), 2.99 – 2.87 (m, 8H), 2.75 (t, J = 10.4 Hz, 1H), 2.57 (d, J = 14.0 Hz, 3H), 2.43 – 2.32 (m, 1H), 2.15 (dt, J = 19.4, 8.4 Hz, 4H), 1.99 – 1.91 (m, 1H), 1.75 (t, J = 11.4 Hz, 3H), 1.68 – 1.54 (m, 2H), 1.25 – 1.12 (m, 2H).	782.9	782.8	C
A24	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.07 (d, J = 6.8 Hz, 3H), 7.01 (d, J = 8.5 Hz, 1H), 6.76 – 6.70 (m,	782.9	782.8	C

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	2H), 6.55 (d, J = 8.7 Hz, 2H), 6.45 (dd, J = 8.3, 2.2 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 6.30 (d, J = 7.0 Hz, 1H), 6.11 (s, 1H), 5.03 (dd, J = 13.2, 5.0 Hz, 1H), 4.64 (d, J = 5.1 Hz, 1H), 4.36 (d, J = 8.3 Hz, 1H), 4.26 (d, J = 16.9 Hz, 1H), 4.10 (d, J = 16.9 Hz, 1H), 4.01 – 3.91 (m, 1H), 3.82 (d, J = 11.5 Hz, 1H), 3.56 (t, J = 10.1 Hz, 2H), 3.33 (s, 4H), 3.26 – 3.13 (m, 3H), 2.92 – 2.82 (m, 3H), 2.75 (t, J = 10.4 Hz, 1H), 2.57 (d, J = 14.7 Hz, 3H), 2.45 – 2.31 (m, 1H), 2.26 – 2.04 (m, 4H), 2.01 – 1.89 (m, 1H), 1.69 (ddd, J = 46.1, 28.1, 9.8 Hz, 5H), 1.27 – 1.11 (m, 2H).			
A25	^{1}H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 9.13 (s, 1H), 8.19 (s, 1H), 7.46 (s, 1H), 7.13 (t, J = 7.6 Hz, 3H), 7.00 (s, 1H), 6.82 (d, J = 6.7 Hz, 2H), 6.65 (d, J = 8.3 Hz, 1H), 6.59 (s, 1H), 6.53 (d, J = 8.5 Hz, 2H), 6.48 (d, J = 8.2 Hz, 1H), 6.20 (d, J = 8.5 Hz, 2H), 5.07 (dd, J = 13.0, 5.2 Hz, 1H), 4.45 (s, 2H), 4.33 (d, J = 16.9 Hz, 1H), 4.20 (d, J = 17.0 Hz, 1H), 4.12 (d, J = 4.7 Hz, 1H), 3.86 (t, J = 7.6 Hz, 1H), 3.46 – 3.41 (m, 3H), 3.02 (s, 4H), 2.98 – 2.78 (m, 6H), 2.64 (d, J = 26.2 Hz, 1H), 2.34 (t, J = 16.7 Hz, 3H), 2.17 – 2.05 (m, 1H), 1.93 (ddd, J = 22.8, 14.6, 8.6 Hz, 6H), 1.71 – 1.57 (m, 6H), 1.33 (dd, J = 12.6, 7.2 Hz, 1H).	808.0	808.0	C
A26	^{1}H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 9.11 (s, 1H), 7.46 (s, 1H), 7.19 – 7.07 (m, 3H), 7.00 (s, 1H), 6.82 (d, J = 6.4 Hz, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.59 (s, 1H), 6.53 (d, J = 8.8 Hz, 2H), 6.48 (dd, J = 8.4, 2.4 Hz, 1H), 6.20 (d, J = 8.4 Hz, 2H), 5.07 (dd, J = 13.2, 4.8 Hz, 1H), 4.49 – 4.42 (m, 2H), 4.33 (d, J = 16.8 Hz, 1H), 4.20 (d, J = 17.2 Hz, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.86 (d, J = 7.2 Hz, 1H), 3.45 (d, J = 8.0 Hz, 2H), 3.03 (s, 4H), 2.96 – 2.78 (m, 5H), 2.58 (d, J = 19.2 Hz, 2H), 2.34 (dd, J = 21.6, 8.0 Hz, 3H), 2.10 (dd, J = 12.0, 6.4 Hz, 1H), 2.01 – 1.84 (m, 6H), 1.73 – 1.54 (m, 7H), 1.33 (dd, J = 12.4, 8.4 Hz, 1H).	808.0	808.0	C
A27	^{1}H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 7.17 – 7.09 (m, 3H), 6.94 (d, J = 8.4 Hz, 2H),	739.9	739.8	C

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	6.82 (d, J = 6.4 Hz, 2H), 6.66 – 6.56 (m, 4H), 6.55 – 6.45 (m, 3H), 6.19 (d, J = 8.8 Hz, 2H), 5.64 (d, J = 7.6 Hz, 1H), 4.29 – 4.20 (m, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.89 – 3.82 (m, 1H), 3.45 – 3.38 (m, 1H), 3.31 – 3.23 (m, 2H), 3.05 – 2.88 (m, 8H), 2.78 – 2.68 (m, 1H), 2.61 – 2.53 (m, 2H), 2.37 – 2.29 (m, 3H), 2.13 – 1.83 (m, 6H), 1.72 – 1.51 (m, 9H), 1.32 (dd, J = 12.4, 8.4 Hz, 1H).			
A28	^{1}H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 7.17 – 7.08 (m, 3H), 6.94 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 6.4 Hz, 2H), 6.66 – 6.45 (m, 7H), 6.19 (d, J = 8.8 Hz, 2H), 5.63 (d, J = 7.6 Hz, 1H), 4.29 – 4.19 (m, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.85 (t, J = 7.6 Hz, 1H), 3.45 – 3.39 (m, 2H), 3.31 – 3.25 (m, 2H), 3.06 – 2.88 (m, 8H), 2.78 – 2.66 (m, 1H), 2.63 – 2.52 (m, 2H), 2.34 – 2.24 (m, 3H), 2.13 – 2.05 (m, 2H), 2.01 – 1.79 (m, 4H), 1.69 – 1.52 (m, 8H), 1.31 (dd, J = 12.4, 8.4 Hz, 1H).	739.9	739.8	C
A29	^{1}H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 7.19 – 7.06 (m, 3H), 6.94 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 7.2 Hz, 2H), 6.66 – 6.56 (m, 4H), 6.54 – 6.45 (m, 3H), 6.20 (d, J = 8.4 Hz, 2H), 5.62 (d, J = 7.2 Hz, 1H), 4.28 – 4.22 (m, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.84 (t, J = 7.6 Hz, 1H), 3.44 – 3.40 (m, 2H), 3.30 – 3.25 (m, 2H), 3.05 – 2.99 (m, 4H), 2.97 – 2.87 (m, 4H), 2.79 – 2.66 (m, 2H), 2.62 – 2.58 (m, 1H), 2.32 – 2.25 (m, 3H), 2.13 – 2.04 (m, 2H), 1.98 – 1.81 (m, 4H), 1.71 – 1.68 (m, 1H), 1.64 – 1.51 (m, 7H), 1.34 – 1.26 (m, 1H).	739.9	739.8	C
A30	^{1}H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 8.20 (s, 1H), 7.08 (d, J = 6.8 Hz, 3H), 6.94 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 7.4 Hz, 2H), 6.62 – 6.54 (m, 4H), 6.47 (d, J = 8.2 Hz, 1H), 6.22 – 6.13 (m, 2H), 5.64 (d, J = 7.6 Hz, 1H), 4.66 (d, J = 5.6 Hz, 1H), 4.25 (s, 1H), 3.27 – 3.23 (m, 2H), 2.95 (s, 4H), 2.88 (s, 3H), 2.73 (s, 3H), 2.59 (s, 1H), 2.41 – 2.39 (m, 1H), 2.31 (d, J = 12.2 Hz, 1H), 2.11 (s, 1H), 1.98 (d, J = 7.8 Hz, 4H), 1.85 (d, J = 8.0 Hz, 1H), 1.65 (d,	771.9	771.8	D

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	J = 11.0 Hz, 4H), 1.55 (s, 3H), 1.43 (d, J = 9.8 Hz, 2H), 1.24 (s, 4H).			
A31	^{1}H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.21 (s, 1H), 7.08 (d, J = 7.2 Hz, 3H), 6.94 (d, J = 8.2 Hz, 2H), 6.75 (d, J = 6.0 Hz, 2H), 6.60 (d, J = 8.6 Hz, 3H), 6.54 (s, 1H), 6.47 (d, J = 8.6 Hz, 1H), 6.25 – 6.10 (m, 2H), 5.64 (d, J = 7.2 Hz, 1H), 4.66 (d, J = 5.4 Hz, 1H), 4.25 (s, 1H), 3.26 – 3.22 (m, 3H), 2.95 (s, 2H), 2.88 (s, 3H), 2.81 – 2.69 (m, 4H), 2.58 (d, J = 12.2 Hz, 1H), 2.41 (s, 2H), 2.30 (s, 1H), 2.10 (s, 2H), 2.02 – 1.96 (m, 3H), 1.85 (d, J = 7.8 Hz, 1H), 1.64 (s, 4H), 1.54 (d, J = 6.2 Hz, 3H), 1.41 (d, J = 10.8 Hz, 2H), 1.24 (s, 3H), 1.06 – 0.77 (m, 1H).	771.9	771.8	D
A32	^{1}H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 9.13 (s, 1H), 8.16 (s, 1H), 7.08 (d, J = 6.6 Hz, 3H), 6.94 (d, J = 10.0 Hz, 2H), 6.76 (d, J = 7.6 Hz, 2H), 6.60 (d, J = 8.4 Hz, 3H), 6.54 (s, 1H), 6.48 (s, 1H), 6.23 – 6.15 (m, 2H), 5.65 (d, J = 7.6 Hz, 1H), 5.32 (s, 2H), 4.67 (s, 1H), 4.26 (s, 1H), 2.95 (s, 3H), 2.89 – 2.84 (m, 2H), 2.70 (d, J = 10.2 Hz, 6H), 2.33 (s, 2H), 2.02 (d, J = 7.4 Hz, 4H), 1.87 – 1.80 (m, 1H), 1.67 (s, 3H), 1.57 (s, 3H), 1.46 – 1.41 (m, 3H), 1.26 (s, 4H), 0.85 (s, 2H).	771.9	771.8	D
A33	^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 9.06 (s, 1H), 7.35 (s, 1H), 7.07 (d, J = 6.8 Hz, 4H), 6.76 – 6.71 (m, 2H), 6.59 – 6.53 (m, 2H), 6.45 (dd, J = 8.3, 2.3 Hz, 1H), 6.38 (d, J = 8.5 Hz, 1H), 6.32 (d, J = 8.6 Hz, 1H), 6.13 (s, 1H), 5.09 (dd, J = 13.2, 5.2 Hz, 1H), 4.65 (d, J = 4.9 Hz, 1H), 4.55 (s, 2H), 4.37 (d, J = 17.1 Hz, 1H), 4.25 (d, J = 17.0 Hz, 1H), 3.60 (s, 2H), 3.26 – 3.18 (m, 2H), 3.00 – 2.85 (m, 8H), 2.61 (dd, J = 21.4, 17.9 Hz, 4H), 2.37 (dd, J = 19.3, 7.2 Hz, 2H), 2.24 – 2.09 (m, 3H), 1.98 (dd, J = 6.8, 3.7 Hz, 2H), 1.89 (dd, J = 13.0, 6.8 Hz, 1H), 1.79 (d, J = 9.7 Hz, 3H), 1.63 – 1.56 (m, 1H), 1.33 – 1.20 (m, 3H).	781.9	781.8	C

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
A34	^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.06 (s, 1H), 7.22 – 6.92 (m, 5H), 6.73 (d, J = 5.8 Hz, 2H), 6.60 – 6.51 (m, 2H), 6.49 – 6.42 (m, 1H), 6.40 – 6.28 (m, 2H), 6.13 (t, J = 6.0 Hz, 1H), 5.03 (d, J = 13.0 Hz, 1H), 4.65 (d, J = 5.2 Hz, 1H), 4.28 – 4.16 (m, 2H), 4.03 – 3.85 (m, 1H), 3.61 (dd, J = 21.7, 12.2 Hz, 3H), 3.15 (d, J = 35.1 Hz, 4H), 3.00 – 2.85 (m, 8H), 2.63 (d, J = 29.1 Hz, 2H), 2.33 (s, 1H), 2.23 – 2.10 (m, 3H), 1.96 (dd, J = 10.7, 5.9 Hz, 2H), 1.85 – 1.73 (m, 3H), 1.58 (dd, J = 11.1, 8.2 Hz, 3H), 1.24 (s, 2H).	782.9	782.2	C
A35	^{1}H NMR (400 MHz, MeOD) δ 7.32 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 7.1 Hz, 3H), 7.03 (d, J = 8.5 Hz, 1H), 6.81 – 6.76 (m, 2H), 6.65 (dd, J = 8.2, 5.4 Hz, 2H), 6.54 (dd, J = 8.4, 2.4 Hz, 1H), 6.29 (d, J = 13.6 Hz, 1H), 6.24 (d, J = 7.5 Hz, 1H), 5.10 (dd, J = 13.3, 5.0 Hz, 1H), 4.80 (d, J = 5.0 Hz, 1H), 4.41 – 4.27 (m, 3H), 4.10 – 4.01 (m, 1H), 3.86 (d, J = 12.1 Hz, 1H), 3.19 – 3.05 (m, 2H), 3.01 (d, J = 22.5 Hz, 6H), 2.89 (dd, J = 13.1, 5.4 Hz, 2H), 2.82 – 2.75 (m, 1H), 2.72 – 2.58 (m, 2H), 2.50 (dd, J = 13.2, 4.7 Hz, 1H), 2.35 (d, J = 7.0 Hz, 2H), 2.28 (dd, J = 22.3, 10.0 Hz, 2H), 2.20 – 2.11 (m, 1H), 1.88 (dd, J = 7.6, 3.8 Hz, 3H), 1.73 (dt, J = 14.3, 7.0 Hz, 2H), 1.38 (ddd, J = 25.5, 18.7, 13.9 Hz, 5H).	800.9	800.9	D
A36	^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.05 (s, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.07 (d, J = 11.5 Hz, 3H), 6.74 (d, J = 7.6 Hz, 2H), 6.55 (d, J = 11.7 Hz, 2H), 6.45 (d, J = 10.5 Hz, 1H), 6.34 (dd, J = 25.3, 8.3 Hz, 2H), 6.12 (d, J = 1.1 Hz, 1H), 5.09 (dd, J = 13.2, 4.8 Hz, 1H), 4.65 (d, J = 5.0 Hz, 1H), 4.56 (s, 2H), 4.38 (d, J = 17.1 Hz, 1H), 4.22 (d, J = 17.1 Hz, 1H), 3.57 (d, J = 8.0 Hz, 2H), 3.25 – 3.19 (m, 1H), 2.98 – 2.81 (m, 7H), 2.57 (t, J = 11.5 Hz, 4H), 2.45 – 2.35 (m, 2H), 2.18 (dd, J = 24.8, 14.4 Hz, 2H), 1.99 (dd, J = 18.0, 12.5 Hz, 3H), 1.84 – 1.68 (m, 5H), 1.66 – 1.49 (m, 2H), 1.33 – 1.14 (m, 3H).	781.9	781.8	C

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
A37	^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 9.06 (s, 1H), 7.35 – 7.27 (m, 2H), 7.08 (d, J = 6.7 Hz, 3H), 6.74 (d, J = 7.7 Hz, 2H), 6.56 (dd, J = 9.3, 5.3 Hz, 2H), 6.49 – 6.43 (m, 1H), 6.39 (d, J = 8.4 Hz, 1H), 6.32 (d, J = 9.2 Hz, 1H), 6.14 (d, J = 1.4 Hz, 1H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.65 (d, J = 4.3 Hz, 2H), 4.39 (d, J = 17.1 Hz, 1H), 4.23 (d, J = 17.1 Hz, 1H), 3.64 – 3.54 (m, 3H), 3.22 (dd, J = 10.9, 5.9 Hz, 2H), 3.08 (dd, J = 23.1, 8.9 Hz, 3H), 2.96 (s, 3H), 2.88 (dd, J = 17.9, 11.8 Hz, 3H), 2.63 (dd, J = 21.2, 11.2 Hz, 3H), 2.45 – 2.29 (m, 2H), 2.18 (ddd, J = 19.6, 15.1, 6.9 Hz, 3H), 1.97 (dd, J = 18.0, 10.9 Hz, 4H), 1.80 (dd, J = 17.0, 4.3 Hz, 2H), 1.64 – 1.49 (m, 2H), 1.24 (s, 2H).	781.9	781.8	C
A38	^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.05 (s, 1H), 7.43 (s, 1H), 7.06 (dd, J = 12.8, 7.9 Hz, 4H), 6.77 – 6.69 (m, 2H), 6.56 (dd, J = 7.2, 5.5 Hz, 2H), 6.45 (dd, J = 8.2, 2.4 Hz, 1H), 6.33 (dt, J = 8.4, 5.0 Hz, 2H), 6.12 (d, J = 1.7 Hz, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.65 (d, J = 5.0 Hz, 1H), 4.50 (s, 2H), 4.36 (d, J = 17.1 Hz, 1H), 4.23 (d, J = 17.0 Hz, 1H), 3.57 (dd, J = 13.3, 5.1 Hz, 2H), 3.21 (dd, J = 12.5, 6.8 Hz, 2H), 2.95 (s, 3H), 2.93 – 2.79 (m, 3H), 2.60 (dd, J = 30.8, 17.5 Hz, 4H), 2.43 – 2.32 (m, 2H), 2.16 (tdd, J = 23.5, 12.7, 7.4 Hz, 2H), 2.05 – 1.94 (m, 3H), 1.91 – 1.63 (m, 6H), 1.59 (dd, J = 15.2, 6.2 Hz, 1H), 1.27 – 1.17 (m, 3H).	781.9	781.8	C
A39	^{1}H NMR (400 MHz, MeOD) δ 7.31 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 6.8 Hz, 3H), 7.03 (d, J = 8.5 Hz, 1H), 6.81 – 6.76 (m, 2H), 6.65 (dd, J = 8.3, 5.3 Hz, 2H), 6.54 (dd, J = 8.3, 2.4 Hz, 1H), 6.29 (d, J = 13.6 Hz, 1H), 6.23 (d, J = 7.4 Hz, 1H), 5.10 (dd, J = 13.3, 5.0 Hz, 1H), 4.80 (d, J = 5.6 Hz, 1H), 4.42 – 4.25 (m, 3H), 4.05 (dd, J = 10.4, 8.9 Hz, 1H), 3.91 – 3.75 (m, 1H), 3.28 (s, 1H), 3.15 – 2.94 (m, 8H), 2.93 – 2.83 (m, 2H), 2.83 – 2.75 (m, 1H), 2.71 – 2.58 (m, 2H), 2.49 (dd, J = 13.1, 4.6 Hz, 1H), 2.35 (d, J = 6.9 Hz, 2H), 2.31 – 2.22 (m, 2H), 2.18 – 2.11 (m, 1H), 1.88 (dd, J =	800.9	800.9	D

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	16.5, 5.6 Hz, 3H), 1.72 (dd, J = 16.4, 7.1 Hz, 2H), 1.37 (ddd, J = 24.1, 18.3, 6.1 Hz, 4H).			
A40	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.24 (s, 1H), 7.20 – 7.08 (m, 4H), 7.01 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 6.6 Hz, 2H), 6.65 – 6.57 (m, 2H), 6.49 – 6.44 (m, 1H), 6.17 (d, J = 8.4 Hz, 2H), 6.05 (d, J = 8.4 Hz, 2H), 5.08 – 4.97 (m, 1H), 4.35 (d, J = 10.2 Hz, 1H), 4.28 (s, 1H), 4.24 (s, 1H), 4.14 – 4.06 (m, 2H), 3.99 – 3.92 (m, 1H), 3.90 – 3.74 (m, 3H), 3.74 – 3.70 (m, 1H), 3.65 – 3.59 (m, 1H), 3.58 – 3.53 (m, 1H), 3.53 – 3.46 (m, 1H), 3.03 – 2.83 (m, 5H), 2.81 – 2.63 (m, 2H), 2.42 – 2.22 (m, 5H), 2.16 – 2.02 (m, 2H), 2.00 – 1.61 (m, 5H).	780.9	780.9	A
A41	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.24 (s, 1H), 7.20 – 7.08 (m, 4H), 7.01 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 6.6 Hz, 2H), 6.65 – 6.57 (m, 2H), 6.49 – 6.44 (m, 1H), 6.17 (d, J = 8.4 Hz, 2H), 6.05 (d, J = 8.4 Hz, 2H), 5.08 – 4.97 (m, 1H), 4.35 (d, J = 10.2 Hz, 1H), 4.28 (s, 1H), 4.24 (s, 1H), 4.14 – 4.06 (m, 2H), 3.99 – 3.92 (m, 1H), 3.90 – 3.74 (m, 3H), 3.74 – 3.70 (m, 1H), 3.65 – 3.59 (m, 1H), 3.58 – 3.53 (m, 1H), 3.53 – 3.46 (m, 1H), 3.03 – 2.83 (m, 5H), 2.81 – 2.63 (m, 2H), 2.42 – 2.22 (m, 5H), 2.16 – 2.02 (m, 2H), 2.00 – 1.61 (m, 5H).	780.9	780.9	A
A42	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.24 (s, 1H), 7.20 – 7.08 (m, 4H), 7.01 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 6.6 Hz, 2H), 6.65 – 6.57 (m, 2H), 6.49 – 6.44 (m, 1H), 6.17 (d, J = 8.4 Hz, 2H), 6.05 (d, J = 8.4 Hz, 2H), 5.08 – 4.97 (m, 1H), 4.35 (d, J = 10.2 Hz, 1H), 4.28 (s, 1H), 4.24 (s, 1H), 4+J6.14 – 4.06 (m, 2H), 3.99 – 3.92 (m, 1H), 3.90 – 3.74 (m, 3H), 3.74 – 3.70 (m, 1H), 3.65 – 3.59 (m, 1H), 3.58 –+K:X 3.53 (m, 1H), 3.53 – 3.46 (m, 1H), 3.03 – 2.83 (m, 5H), 2.81 – 2.63 (m, 2H), 2.42 – 2.22 (m, 5H), 2.16 – 2.02 (m, 2H), 2.00 – 1.61 (m, 5H).	780.9	780.9	D
A43	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.25 (s, 1H), 7.17 – 7.07 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.82 (d, J = 6.6 Hz, 2H),	780.9	780.9	A

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	6.65 – 6.57 (m, 2H), 6.50 – 6.45 (m, 1H), 6.17 (d, J = 8.4 Hz, 2H), 6.05 (d, J = 8.4 Hz, 2H), 5.06 – 4.98 (m, 1H), 4.32 – 4.19 (m, 2H), 4.19 – 4.07 (m, 2H), 3.94 – 3.68 (m, 5H), 3.62 (t, J = 7.4 Hz, 2H), 3.58 – 3.45 (m, 3H), 3.04 – 2.82 (m, 6H), 2.82 – 2.71 (m, 1H), 2.69 – 2.65 (m, 1H), 2.42 – 2.21 (m, 4H), 2.16 – 2.01 (m, 2H), 2.01 – 1.91 (m, 1H), 1.90 – 1.80 (m, 1H), 1.79 – 1.64 (m, 2H).			
A44	^{1}H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 8.17 (s, 1H), 7.20 – 7.06 (m, 3H), 7.01 (d, J = 8.2 Hz, 2H), 6.82 (d, J = 6.8 Hz, 2H), 6.70 – 6.57 (m, 4H), 6.57 – 6.44 (m, 3H), 6.19 (d, J = 8.4 Hz, 2H), 5.85 (d, J = 7.6 Hz, 1H), 4.35 – 4.24 (m, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.86 – 3.78 (m, 1H), 3.42 (t, J = 7.8 Hz, 1H), 3.30 – 3.24 (m, 1H), 3.06 – 2.90 (m, 7H), 2.78 – 2.69 (m, 1H), 2.62 – 2.52 (m, 3H), 2.45 – 2.26 (m, 3H), 2.17 – 2.04 (m, 5H), 1.92 – 1.55 (m, 8H), 1.36 – 1.26 (m, 1H).	787.9	787.8	E
A45	^{1}H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 8.21 (s, 1H), 7.20 – 7.05 (m, 3H), 7.01 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 6.8 Hz, 2H), 6.68 – 6.56 (m, 4H), 6.56 – 6.43 (m, 3H), 6.19 (d, J = 8.2 Hz, 2H), 5.85 (d, J = 7.2 Hz, 1H), 4.33 – 4.25 (m, 1H), 4.12 (d, J = 4.2 Hz, 1H), 3.86 – 3.78 (m, 1H), 3.42 (t, J = 7.6 Hz, 1H), 3.27 (d, J = 10.0 Hz, 1H), 3.07 – 2.88 (m, 7H), 2.78 – 2.68 (m, 1H), 2.63 – 2.52 (m, 3H), 2.44 – 2.26 (m, 3H), 2.19 – 2.03 (m, 5H), 1.92 – 1.54 (m, 8H), 1.35 – 1.26 (m, 1H).	787.9	787.8	E
A46	^{1}H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 8.21 (s, 1H), 7.08 (t, J = 6.6 Hz, 3H), 6.94 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 7.6 Hz, 2H), 6.60 (d, J = 8.6 Hz, 3H), 6.55 (d, J = 8.4 Hz, 1H), 6.49 – 6.44 (m, 1H), 6.22 – 6.13 (m, 2H), 5.64 (d, J = 7.4 Hz, 1H), 4.66 (d, J = 5.2 Hz, 1H), 4.25 (s, 1H), 2.95 (s, 4H), 2.89 (d, J = 11.8 Hz, 4H), 2.80 (s, 1H), 2.76 – 2.68 (m, 2H), 2.62 – 2.54 (m, 1H), 2.40 (d, J = 6.4 Hz, 2H), 2.29 (s, 1H), 2.20 – 2.06 (m, 2H), 2.02 – 1.91 (m, 5H), 1.87 – 1.77 (m, 1H), 1.65 (d, J	771.4	771.4	D

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	= 10.6 Hz, 5H), 1.55 (s, 2H), 1.43 (d, J = 9.4 Hz, 2H), 1.24 (s, 4H).			
A47	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.97 (s, 1H), 7.29 (t, J = 7.4 Hz, 2H), 7.25 – 7.07 (m, 5H), 7.01 (dd, J = 8.3, 3.8 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.42 (d, J = 11.9 Hz, 2H), 6.29 (s, 1H), 6.17 (s, 1H), 5.03 (dd, J = 13.3, 5.1 Hz, 1H), 4.36 – 4.24 (m, 3H), 4.10 (d, J = 17.0 Hz, 1H), 3.96 (dd, J = 17.1, 7.8 Hz, 2H), 3.84 (s, 3H), 3.49 (dd, J = 13.1, 6.0 Hz, 2H), 3.39 (d, J = 5.5 Hz, 3H), 3.13 (s, 1H), 2.87 (d, J = 12.5 Hz, 3H), 2.75 – 2.60 (m, 4H), 2.26 (dd, J = 15.2, 8.1 Hz, 3H), 1.93 (s, 2H), 1.72 (d, J = 8.8 Hz, 4H), 1.29 (s, 2H), 0.85 (t, J = 6.6 Hz, 2H).	810.4	810.3	C
A48	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.35 (s, 1H), 7.43 – 7.22 (m, 3H), 7.17 (td, J = 7.3, 3.7 Hz, 4H), 7.01 (dd, J = 8.3, 4.3 Hz, 1H), 6.55 (d, J = 8.2 Hz, 1H), 6.45 – 6.39 (m, 2H), 6.29 (s, 1H), 6.17 (s, 1H), 5.03 (dd, J = 13.2, 5.0 Hz, 1H), 4.30 (dd, J = 25.0, 8.7 Hz, 3H), 4.10 (d, J = 16.9 Hz, 1H), 3.98 – 3.92 (m, 1H), 3.78 (d, J = 6.9 Hz, 2H), 3.49 – 3.43 (m, 4H), 3.14 (d, J = 8.5 Hz, 2H), 2.89 (dd, J = 10.5, 7.0 Hz, 3H), 2.66 (ddd, J = 31.2, 17.1, 10.5 Hz, 4H), 2.45 – 2.27 (m, 3H), 2.22 (d, J = 7.3 Hz, 2H), 2.09 (dd, J = 15.9, 8.7 Hz, 2H), 1.91 (dd, J = 27.4, 5.9 Hz, 3H), 1.76 – 1.59 (m, 5H).	810.4	810.3	C
A49	^{1}H NMR (400 MHz, MeOD) δ 7.14 (d, J = 7.0 Hz, 3H), 7.12 – 7.03 (m, 4H), 6.88 – 6.81 (m, 2H), 6.75 (d, J = 8.5 Hz, 2H), 6.72 – 6.66 (m, 2H), 6.62 – 6.51 (m, 3H), 4.35 (d, J = 5.3 Hz, 1H), 4.29 (dd, J = 11.8, 4.9 Hz, 1H), 4.20 – 4.14 (m, 1H), 3.76 – 3.63 (m, 3H), 3.60 – 3.50 (m, 2H), 3.46 – 3.41 (m, 2H), 3.29 (d, J = 6.8 Hz, 2H), 3.17 – 2.99 (m, 4H), 2.96 – 2.87 (m, 1H), 2.82 – 2.75 (m, 2H), 2.38 – 2.19 (m, 3H), 2.10 (d, J = 13.4 Hz, 3H), 2.02 – 1.92 (m, 5H), 1.84 (d, J = 8.4 Hz, 1H), 1.67 (dd, J = 12.5, 9.1 Hz, 1H), 1.39 – 1.29 (m, 3H).	739.4	739.3	C
A50	^{1}H NMR (400 MHz, MeOD) δ 7.16 – 7.04 (m, 5H), 6.82 (dd, J = 7.3, 2.0 Hz, 2H), 6.73	739.4	739.3	C

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	(dd, J = 11.8, 8.5 Hz, 3H), 6.66 (dd, J = 9.1, 5.6 Hz, 3H), 6.54 (dd, J = 8.3, 2.5 Hz, 1H), 6.33 (d, J = 8.6 Hz, 2H), 4.29 (dd, J = 11.8, 4.9 Hz, 1H), 4.20 (d, J = 5.0 Hz, 1H), 4.14 – 4.09 (m, 1H), 3.62 (dd, J = 19.5, 11.2 Hz, 3H), 3.25 (d, J = 6.7 Hz, 2H), 3.12 (d, J = 4.7 Hz, 5H), 3.04 (d, J = 5.7 Hz, 2H), 2.90 – 2.72 (m, 4H), 2.38 – 2.30 (m, 1H), 2.27 – 2.17 (m, 2H), 2.08 (d, J = 15.6 Hz, 2H), 1.96 (d, J = 13.0 Hz, 3H), 1.78 (tt, J = 13.4, 6.7 Hz, 5H), 1.55 (dd, J = 12.6, 8.8 Hz, 1H), 1.33 (d, J = 16.2 Hz, 2H).			
A51	^{1}H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 7.16 – 7.10 (m, 3H), 6.95 – 6.89 (m, 2H), 6.82 (d, J = 7.2 Hz, 2H), 6.67 – 6.58 (m, 4H), 6.54 – 6.46 (m, 3H), 6.20 (d, J = 8.4 Hz, 2H), 5.62 (d, J = 7.6 Hz, 1H), 4.29 – 4.20 (m, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.84 (d, J = 7.6 Hz, 1H), 3.44 – 3.40 (m, 2H), 3.30 – 3.26 (m, 2H), 3.05 – 2.92 (m, 8H), 2.77 – 2.67 (m, 1H), 2.62 – 2.56 (m, 1H), 2.33 – 2.26 (m, 3H), 2.14 – 2.06 (m, 2H), 2.00 – 1.84 (m, 4H), 1.68 – 1.52 (m, 9H), 1.31 (dd, J = 12.4, 8.4 Hz, 1H).	739.4	739.3	C
A52	^{1}H NMR (400 MHz, MeOD) δ 7.31 (d, J = 8.3 Hz, 1H), 7.05 (dt, J = 12.0, 6.0 Hz, 4H), 6.78 – 6.72 (m, 2H), 6.64 (d, J = 8.3 Hz, 2H), 6.54 – 6.48 (m, 2H), 6.43 (dd, J = 8.5, 2.1 Hz, 1H), 6.21 (d, J = 2.1 Hz, 1H), 5.10 (dd, J = 13.2, 5.1 Hz, 1H), 4.78 (d, J = 5.3 Hz, 1H), 4.40 – 4.34 (m, 2H), 4.05 (dd, J = 12.5, 6.7 Hz, 2H), 3.86 (d, J = 11.8 Hz, 1H), 3.61 (t, J = 8.0 Hz, 1H), 3.23 (s, 1H), 3.15 (s, 3H), 3.03 (s, 3H), 3.00 (d, J = 5.5 Hz, 2H), 2.89 (dd, J = 12.8, 4.9 Hz, 2H), 2.82 – 2.76 (m, 1H), 2.74 – 2.66 (m, 1H), 2.48 (d, J = 7.2 Hz, 2H), 2.30 (s, 1H), 2.20 – 2.05 (m, 3H), 1.89 (d, J = 18.7 Hz, 1H), 1.80 (s, 4H), 1.65 (s, 2H), 1.49 (dd, J = 12.6, 8.3 Hz, 1H), 1.33 (d, J = 18.0 Hz, 5H).	838.4	838.4	C
A53	^{1}H NMR (400 MHz, MeOD) δ 7.35 (d, J = 8.3 Hz, 1H), 7.12 – 7.04 (m, 4H), 6.75 (dd, J = 6.6, 2.8 Hz, 2H), 6.69 – 6.55 (m, 4H), 6.51 (dd, J = 8.4, 2.6 Hz, 1H), 6.32 (s, 1H), 5.10 (dd, J = 13.3, 5.0 Hz, 1H), 4.44 – 4.39 (m,	838.4	838.4	C

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	1H), 4.36 (d, J = 9.1 Hz, 1H), 4.09 (d, J = 6.3 Hz, 2H), 3.63 (t, J = 7.8 Hz, 1H), 3.48 (d, J = 16.7 Hz, 1H), 3.26 (s, 4H), 3.06 (s, 3H), 3.03 – 2.86 (m, 5H), 2.85 – 2.72 (m, 3H), 2.56 – 2.36 (m, 2H), 2.30 (dd, J = 11.2, 6.6 Hz, 1H), 2.24 – 2.15 (m, 2H), 2.05 (s, 1H), 1.87 (s, 4H), 1.73 – 1.51 (m, 3H), 1.38 – 1.29 (m, 5H).			
A54	^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.05 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 6.6 Hz, 3H), 6.72 (d, J = 9.1 Hz, 2H), 6.56 (d, J = 8.5 Hz, 2H), 6.45 (d, J = 10.7 Hz, 1H), 6.37 (d, J = 8.5 Hz, 1H), 6.31 (d, J = 6.3 Hz, 1H), 6.11 (s, 1H), 5.08 (dd, J = 12.0, 4.2 Hz, 1H), 4.64 (d, J = 5.3 Hz, 1H), 4.52 (s, 2H), 4.37 (d, J = 17.0 Hz, 1H), 4.21 (d, J = 16.9 Hz, 1H), 3.88 (t, J = 7.8 Hz, 1H), 3.47 – 3.42 (m, 1H), 3.20 (dd, J = 12.9, 6.6 Hz, 1H), 3.08 (s, 4H), 2.94 (s, 3H), 2.88 (dd, J = 19.0, 11.1 Hz, 4H), 2.64 (d, J = 25.1 Hz, 2H), 2.34 (d, J = 7.0 Hz, 2H), 2.22 – 2.14 (m, 1H), 2.00 (d, J = 15.9 Hz, 2H), 1.89 (dd, J = 27.6, 14.3 Hz, 4H), 1.71 – 1.64 (m, 4H), 1.60 (d, J = 9.6 Hz, 4H), 1.39 – 1.22 (m, 2H).	837.4	837.4	D
A55	^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.41 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.06 (s, 3H), 6.72 (d, J = 6.2 Hz, 2H), 6.55 (d, J = 8.2 Hz, 2H), 6.45 (d, J = 8.6 Hz, 1H), 6.36 (d, J = 8.7 Hz, 1H), 6.32 (s, 1H), 6.11 (s, 1H), 5.06 (s, 1H), 4.64 (d, J = 4.8 Hz, 1H), 4.52 (s, 2H), 4.37 (d, J = 17.6 Hz, 1H), 4.21 (d, J = 16.8 Hz, 1H), 3.88 (s, 1H), 3.08 (s, 4H), 2.94 (s, 3H), 2.88 – 2.76 (m, 4H), 2.67 (s, 2H), 2.32 (s, 3H), 2.20 (s, 2H), 1.99 (s, 2H), 1.97 – 1.90 (m, 4H), 1.65 (s, 4H), 1.61 (s, 4H), 1.35 (s, 1H), 1.24 (s, 1H).	837.4	837.4	D
A56	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.05 (s, 1H), 7.06 (t, J = 5.8 Hz, 4H), 6.93 (s, 1H), 6.74 – 6.70 (m, 2H), 6.55 (d, J = 8.2 Hz, 2H), 6.45 (dd, J = 8.4, 2.5 Hz, 1H), 6.36 (d, J = 8.4 Hz, 1H), 6.31 (d, J = 7.9 Hz, 1H), 6.11 (s, 1H), 5.07 – 4.99 (m, 1H), 4.64 (d, J = 4.9	838.4	838.4	C

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	Hz, 1H), 4.35 – 3.99 (m, 4H), 3.90 (s, 3H), 3.45 (s, 1H), 3.20 (d, J = 14.6 Hz, 2H), 3.08 (s, 4H), 2.94 (s, 3H), 2.67 (d, J = 1.8 Hz, 2H), 2.33 (d, J = 1.8 Hz, 3H), 2.11 (d, J = 28.9 Hz, 3H), 1.96 (d, J = 5.5 Hz, 3H), 1.65 (s, 4H), 1.60 (s, 4H), 1.35 (s, 1H), 1.24 (s, 1H).			
A57	^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.06 (s, 1H), 7.19 (s, 1H), 7.07 (d, J = 6.6 Hz, 4H), 6.75 – 6.69 (m, 2H), 6.58 – 6.53 (m, 2H), 6.45 (dd, J = 8.3, 2.4 Hz, 1H), 6.36 (t, J = 10.9 Hz, 2H), 6.13 (s, 1H), 5.04 (dd, J = 13.3, 4.9 Hz, 1H), 4.65 (d, J = 5.1 Hz, 1H), 4.31 (d, J = 14.0 Hz, 2H), 4.22 (d, J = 20.4 Hz, 3H), 3.98 (s, 2H), 3.53 (d, J = 53.1 Hz, 5H), 3.22 (d, J = 13.1 Hz, 3H), 3.10 (s, 5H), 2.94 (s, 3H), 2.89 (d, J = 11.8 Hz, 3H), 2.64 (d, J = 27.3 Hz, 2H), 2.34 (d, J = 12.2 Hz, 1H), 2.22 – 2.06 (m, 2H), 1.96 (d, J = 5.3 Hz, 1H), 1.65 (d, J = 13.9 Hz, 6H).	838.4	838.4	C
A58	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.85 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.42 – 8.06 (m, 2H), 7.86 (d, J = 8.8 Hz, 1H), 7.40 (dd, J = 8.8, 2.8 Hz, 1H), 7.22 – 7.05 (m, 3H), 6.83 (d, J = 6.4 Hz, 2H), 6.67 – 6.42 (m, 5H), 6.20 (d, J = 8.8 Hz, 2H), 4.82 – 4.68 (m, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.70 – 3.13 (m, 9H), 3.01 – 2.73 (m, 3H), 2.61 – 2.52 (m, 1H), 2.49 – 2.42 (m, 4H), 2.24 – 1.92 (m, 5H), 1.80 – 1.55 (m, 4H), 1.25 – 1.06 (m, 2H).	713.4	713.4	
A59	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.78 (s, 1H), 8.35 (s, 1H), 7.18 – 7.06 (m, 3H), 6.98 (t, J = 8.8 Hz, 1H), 6.82 (d, J = 6.6 Hz, 2H), 6.67 – 6.58 (m, 2H), 6.55 – 6.37 (m, 5H), 6.19 (d, J = 8.6 Hz, 2H), 5.99 (d, J = 7.8 Hz, 1H), 4.36 – 4.25 (m, 1H), 4.12 (d, J = 4.6 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.43 – 3.40 (m, 1H), 3.29 – 3.25 (m, 1H), 3.12 – 2.78 (m, 9H), 2.77 – 2.65 (m, 1H), 2.62 – 2.53 (m, 2H), 2.32 – 2.25 (m, 2H), 2.14 – 2.03 (m, 2H), 2.01 – 1.79 (m, 4H), 1.73 – 1.65 (m, 1H), 1.64 – 1.50 (m, 8H), 1.36 – 1.26 (m, 1H).	757.4	757.4	
A60	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.78 (s, 1H), 8.35 (s, 1H), 7.18 – 7.06 (m, 3H), 6.98	757.4	757.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	(t, J = 8.8 Hz, 1H), 6.82 (d, J = 6.6 Hz, 2H), 6.67 – 6.58 (m, 2H), 6.55 – 6.37 (m, 5H), 6.19 (d, J = 8.6 Hz, 2H), 5.99 (d, J = 7.8 Hz, 1H), 4.36 – 4.25 (m, 1H), 4.12 (d, J = 4.6 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.43 – 3.40 (m, 1H), 3.29 – 3.25 (m, 1H), 3.12 – 2.78 (m, 9H), 2.77 – 2.65 (m, 1H), 2.62 – 2.53 (m, 2H), 2.32 – 2.25 (m, 2H), 2.14 – 2.03 (m, 2H), 2.01 – 1.79 (m, 4H), 1.73 – 1.65 (m, 1H), 1.64 – 1.50 (m, 8H), 1.36 – 1.26 (m, 1H).			
A61	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.78 (s, 1H), 8.35 (s, 1H), 7.18 – 7.06 (m, 3H), 6.98 (t, J = 8.8 Hz, 1H), 6.82 (d, J = 6.6 Hz, 2H), 6.67 – 6.58 (m, 2H), 6.55 – 6.37 (m, 5H), 6.19 (d, J = 8.6 Hz, 2H), 5.99 (d, J = 7.8 Hz, 1H), 4.36 – 4.25 (m, 1H), 4.12 (d, J = 4.6 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.43 – 3.40 (m, 1H), 3.29 – 3.25 (m, 1H), 3.12 – 2.78 (m, 9H), 2.77 – 2.65 (m, 1H), 2.62 – 2.53 (m, 2H), 2.32 – 2.25 (m, 2H), 2.14 – 2.03 (m, 2H), 2.01 – 1.79 (m, 4H), 1.73 – 1.65 (m, 1H), 1.64 – 1.50 (m, 8H), 1.36 – 1.26 (m, 1H).	757.4	757.4	
A62	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.78 (s, 1H), 8.35 (s, 1H), 7.18 – 7.06 (m, 3H), 6.98 (t, J = 8.8 Hz, 1H), 6.82 (d, J = 6.6 Hz, 2H), 6.67 – 6.58 (m, 2H), 6.55 – 6.37 (m, 5H), 6.19 (d, J = 8.6 Hz, 2H), 5.99 (d, J = 7.8 Hz, 1H), 4.36 – 4.25 (m, 1H), 4.12 (d, J = 4.6 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.43 – 3.40 (m, 1H), 3.29 – 3.25 (m, 1H), 3.12 – 2.78 (m, 9H), 2.77 – 2.65 (m, 1H), 2.62 – 2.53 (m, 2H), 2.32 – 2.25 (m, 2H), 2.14 – 2.03 (m, 2H), 2.01 – 1.79 (m, 4H), 1.73 – 1.65 (m, 1H), 1.64 – 1.50 (m, 8H), 1.36 – 1.26 (m, 1H).	757.4	757.4	
A63	^{1}H NMR (400M Hz, MeOD) δ 7.15-7.09 (m, 4H), 7.02 (s, 1H), 6.82 (d, J = 7.9 Hz, 2H), 6.71 (d, J = 8.3 Hz, 1H), 6.65 (s, 1H), 6.53 (d, J = 10.9 Hz, 1H), 6.26 (d, J = 8.5 Hz, 2H), 6.15 (d, J = 8.5 Hz, 2H), 5.09 (dd, J = 13.0, 4.9 Hz, 1H), 4.35 (s, 1H), 4.29 (d, J = 13.6 Hz, 1H), 4.17 (d, J = 4.5 Hz, 1H), 3.98 (d, J =	792.5	792.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	9.2 Hz, 1H), 3.83 (s, 1H), 3.49 (s, 2H), 3.42 (s, 2H), 3.09-2.89 (m, 6H), 2.82-2.76 (m, 1H), 2.48 (dd, *J* = 17.3, 9.2 Hz, 1H), 2.24 (dd, *J* = 14.4, 6.3 Hz, 4H), 1.94 (dd, *J* = 9.8, 6.8 Hz, 2H), 1.87-1.76 (m, 4H), 1.57 (ddd, *J* = 29.1, 16.6, 6.1 Hz, 4H), 1.38-1.30 (m, 3H), 1.10-0.99 (m, 2H).			
A64	^{1}H NMR (400M Hz, MeOD) δ 7.14-7.07 (m, 5H), 6.82- 6.77 (m, 2H), 6.74-6.62 (m, 4H), 6.50 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.23 (d, *J* = 8.5 Hz, 2H), 6.12 (d, *J* = 8.5 Hz, 2H), 4.28 (dd, *J* = 11.8, 4.9 Hz, 1H), 4.14 (d, *J* = 4.8 Hz, 1H), 3.49-3.43 (m, 2H), 3.39 (q, *J* = 7.0 Hz, 2H), 3.27 (s, 1H), 3.04-2.93 (m, 2H), 2.78 (dd, *J* = 12.3, 5.3 Hz, 1H), 2.75- 2.64 (m, 3H), 2.40-2.31 (m, 3H), 2.27-2.16 (m, 2H), 2.10 – 1.99 (m, 2H), 1.92 (dd, *J* = 12.6, 4.2 Hz, 3H), 1.81-1.70 (m, 3H), 1.63-1.47 (m, 3H), 1.31 (dd, *J* = 17.4, 4.5 Hz, 2H), 1.09-0.97 (m, 2H).	771.5	771.5	
A65	^{1}H NMR (400M Hz, MeOD) δ 8.55 (s, 1H), 7.13 (d, *J* = 6.9 Hz, 3H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 7.4 Hz, 2H), 6.70 (dd, *J* = 21.1, 12.3 Hz, 4H), 6.53 (d, *J* = 8.3 Hz, 1H), 6.27 (d, *J* = 8.3 Hz, 2H), 6.15 (d, *J* = 8.5 Hz, 2H), 5.37 (s, 1H), 4.28 (dd, *J* = 11.7, 5.0 Hz, 1H), 4.17 (d, *J* = 4.7 Hz, 1H), 3.54-3.46 (m, 2H), 3.44 (d, *J* = 8.9 Hz, 2H), 3.05 -3.00 (m, 1H), 2.85-2.74 (m, 2H), 2.72-2.63 (m, 3H), 2.38 -2.31 (m, 1H), 2.21 (t, *J* = 7.4 Hz, 1H), 2.05 (d, *J* = 4.9 Hz, 1H), 1.98 (d, *J* = 14.5 Hz, 2H), 1.95-1.90 (m, 3H), 1.78 (t, *J* = 9.6 Hz, 3H), 1.61-1.53 (m, 2H), 1.33 (d, *J* = 17.9 Hz, 7H), 1.12 (dd, *J* = 24.0, 9.7 Hz, 2H), 0.92 (t, *J* = 6.1 Hz, 1H).	723.5	723.5	
A66	^{1}H NMR (400M Hz, MeOD) δ 7.11 (t, *J* = 5.9 Hz, 5H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 7.7 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 6.52 (dd, *J* = 8.3, 2.3 Hz, 1H), 4.34 (d, *J* = 5.0 Hz, 1H), 4.27 (dd, *J* = 11.9, 4.9 Hz, 1H), 3.56 (t, *J* = 10.2 Hz, 2H), 3.45 (d, *J* = 25.0 Hz, 4H), 3.25 (d, *J* = 6.9 Hz, 2H), 3.11-3.03 (m, 3H), 2.86 -2.68 (m, 4H), 2.37-2.16 (m, 4H), 2.05 (d, *J* = 11.0 Hz, 4H), 1.92 (dd, *J* = 13.7, 9.6	723.5	723.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	Hz, 4H), 1.85-1.74 (m, 3H), 1.36-1.27 (m, 3H).			
A67	^{1}H NMR (400M Hz, MeOD) δ 7.17 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 7.0 Hz, 3H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 7.7 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.58-6.50 (m, 3H), 4.31 (dd, *J* = 12.3, 4.9 Hz, 2H), 3.49-3.35 (m, 4H), 3.09 -2.98 (m, 2H), 2.89-2.65 (m, 4H), 2.58 (d, *J* = 14.1 Hz, 1H), 2.41-2.11 (m, 7H), 2.02 (d, *J* = 3.9 Hz, 2H), 1.95 (dd, *J* = 12.6, 5.0 Hz, 1H), 1.91-1.86 (m, 2H), 1.84-1.72 (m, 3H), 1.60 (d, *J* = 9.3 Hz, 1H), 1.34-1.27 (m, 4H).	771.5	771.5	
A68	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.67 - 1.77 (m, 2 H) 1.81 - 1.82 (m, 1 H) 1.82 - 2.01 (m, 2 H) 2.03 - 2.47 (m, 5 H) 2.45 - 2.48 (m, 1 H) 2.72 - 2.82 (m, 2 H) 2.87 - 3.07 (m, 6 H) 3.12 - 3.22 (m, 1 H) 3.46 - 3.66 (m, 4 H) 3.70 - 4.02 (m, 6 H) 4.07 - 4.15 (m, 2 H) 4.26 - 4.42 (m, 2 H) 4.96 - 5.10 (m, 1 H) 6.06 (d, *J*=8.56 Hz, 2 H) 6.18 (d, *J*=8.44 Hz, 2 H) 6.48 (dd, *J*=8.25, 2.38 Hz, 1 H) 6.59 - 6.66 (m, 2 H) 6.80 - 6.86 (m, 2 H) 7.02 (d, *J*=8.56 Hz, 1 H) 7.10 - 7.21 (m, 4 H) 7.96 (s, 1 H) 9.10 (s, 1 H) 10.90 - 10.99 (m, 1 H).	780.4	780.4	
A69	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 - 2.14 (m, 4 H) 2.17 - 2.19 (m, 1 H) 2.34 (br d, *J* = 1.22 Hz, 1 H) 3.46 - 3.67 (m, 7 H) 3.69 - 3.92 (m, 7 H) 3.93 - 4.01 (m, 2 H) 4.04 - 4.18 (m, 4 H) 4.19 - 4.45 (m, 5 H) 5.04 (br dd, *J* = 9.29, 4.65 Hz, 2 H) 6.04 - 6.12 (m, 2 H) 6.14 - 6.21 (m, 2 H) 6.44 - 6.51 (m, 1 H) 6.52 - 6.73 (m, 3 H) 6.76 - 6.86 (m, 2 H) 7.02 (br d, *J* = 7.09 Hz, 1 H) 7.09 - 7.23 (m, 5 H) 7.22 - 7.29 (m, 1 H) 9.03 - 9.18 (m, 1 H) 10.87 - 11.05 (m, 1 H).	780.4	780.4	
A70	1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.10 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.19 – 7.07 (m, 3H), 6.83 (d, J = 6.6 Hz, 2H), 6.68 – 6.58 (m, 2H), 6.56 – 6.43 (m, 3H), 6.20 (d, J = 8.5 Hz, 2H), 5.08 (dd, J = 13.2, 5.0 Hz, 1H), 4.59 – 4.46 (m, 2H), 4.37 (d, J = 16.4 Hz, 1H), 4.27 – 4.07 (m, 2H), 3.57 – 3.47 (m, 3H), 3.07 – 2.73 (m,	751.3	751.3	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	6H), 2.66 – 2.55 (m, 1H), 2.44 – 2.30 (m, 1H), 2.27 – 1.52 (m, 15H), 1.27 – 1.04 (m, 2H).			
A71	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.94 (s, 1H), 9.10 (s, 1H), 7.20 – 7.08 (m, 4H), 7.01 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 6.4 Hz, 2H), 6.67 – 6.57 (m, 2H), 6.56 – 6.43 (m, 3H), 6.20 (d, J = 8.4 Hz, 2H), 5.03 (dd, J = 13.2, 5.0 Hz, 1H), 4.40 – 4.32 (m, 1H), 4.26 (d, J = 16.8 Hz, 1H), 4.15 – 4.05 (m, 2H), 4.00 – 3.92 (m, 1H), 3.88 – 3.75 (m, 1H), 3.58 – 3.44 (m, 2H), 3.29 – 3.23 (m, 1H), 3.23 – 3.12 (m, 1H), 3.03 – 2.82 (m, 5H), 2.79 – 2.64 (m, 1H), 2.62 – 2.54 (m, 1H), 2.47 – 2.28 (m, 3H), 2.25 – 2.01 (m, 4H), 1.99 – 1.85 (m, 1H), 1.83 – 1.54 (m, 5H), 1.26 – 1.04 (m, 2H).	752.4	752.4	
A72	^{1}H NMR (400MHz, DMSO-d6) 10.94 (br s, 1H), 8.39 (s, 1H), 7.22 - 7.08 (m, 3H), 7.07 - 7.00 (m, 1H), 6.94 (s, 1H), 6.88 - 6.77 (m, 2H), 6.66 - 6.56 (m, 2H), 6.48 (dd, *J* = 2.3, 8.3 Hz, 1H), 6.34 - 6.15 (m, 2H), 6.13 - 6.01 (m, 2H), 5.11 - 4.97 (m, 1H), 4.32 - 3.98 (m, 5H), 3.95 - 3.70 (m, 5H), 3.62 (br d, *J* = 7.6 Hz, 1H), 3.56 (br d, *J* = 7.5 Hz, 1H), 3.49 (br s, 1H), 3.26 (br s, 1H), 3.21 - 3.11 (m, 2H), 3.05 - 2.85 (m, 5H), 2.76 (br t, *J* = 10.2 Hz, 1H), 2.64 - 2.52 (m, 2H), 2.38 - 2.24 (m, 3H), 2.16 - 2.04 (m, 2H), 2.00 - 1.92 (m, 1H), 1.86 (br dd, *J* = 7.1, 12.7 Hz, 1H), 1.81 - 1.63 (m, 2H).	780.4	780.4	
A73	^{1}H NMR (400MHz, DMSO-d6) 10.94 (br s, 1H), 8.39 (s, 1H), 7.25 - 7.09 (m, 3H), 7.05 (s, 1H), 6.94 (s, 1H), 6.82 (br d, *J*- = 7.1 Hz, 2H), 6.69 - 6.56 (m, 2H), 6.48 (br d, *J* = 8.0 Hz, 1H), 6.35 - 6.15 (m, 2H), 6.13 - 5.97 (m, 2H), 5.03 (br dd, *J* = 4.9, 13.1 Hz, 1H), 4.39 - 4.01 (m, 5H), 3.96 - 3.70 (m, 5H), 3.64 (br d, *J* = 7.5 Hz, 1H), 3.54 (br d, *J* = 7.1 Hz, 1H), 3.49 (br s, 1H), 3.27 - 3.24 (m, 1H), 3.18 (br s, 2H), 3.04 - 2.86 (m, 5H), 2.81 - 2.72 (m, 1H), 2.58 (br d, *J* = 16.5 Hz, 2H), 2.39 - 2.24 (m, 3H), 2.19 - 2.05 (m, 2H), 1.97 (br d, *J* = 5.4	780.4	780.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	Hz, 1H), 1.85 (br dd, *J* = 6.9, 12.2 Hz, 1H), 1.69 (br d, *J* = 10.0 Hz, 2H).			
A74	^{1}H NMR (400MHz, DMSO-d6) 10.98 (s, 1H), 9.10 (s, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.19 - 7.09 (m, 3H), 6.83 (br d, J = 6.7 Hz, 2H), 6.70 - 6.57 (m, 2H), 6.48 (dd, J = 2.4, 8.3 Hz, 1H), 6.18 (d, J = 8.6 Hz, 2H), 6.06 (d, J = 8.6 Hz, 2H), 5.09 (dd, J = 5.1, 13.2 Hz, 1H), 4.60 - 4.49 (m, 2H), 4.38 (d, J = 17.2 Hz, 1H), 4.22 (d, J = 17.2 Hz, 1H), 4.12 (d, J = 4.9 Hz, 1H), 3.88 (br t, J = 7.6 Hz, 1H), 3.82 - 3.70 (m, 2H), 3.62 (d, J = 7.6 Hz, 1H), 3.58 - 3.46 (m, 2H), 3.31 - 3.24 (m, 2H), 3.02 - 2.81 (m, 5H), 2.64 - 2.53 (m, 2H), 2.45 - 2.34 (m, 2H), 2.27 (br dd, J = 7.4, 12.5 Hz, 1H), 2.19 - 1.82 (m, 7H), 1.71 (br d, J = 10.6 Hz, 3H).	779.3	779.3	
A75	^{1}H NMR (400MHz, DMSO-d6) δ10.98 (s, 1H), 9.10 (s, 1H), 7.40 (d, J=7.6 Hz, 1H), 7.27 (d, J=7.6 Hz, 1H), 7.20 - 7.05 (m, 3H), 6.83 (br d, J=6.8 Hz, 2H), 6.69 - 6.58 (m, 2H), 6.48 (dd, J=2.4, 8.3 Hz, 1H), 6.18 (d, J=8.5 Hz, 2H), 6.06 (d, J=8.6 Hz, 2H), 5.09 (dd, J=4.9, 13.4 Hz, 1H), 4.57 - 4.48 (m, 2H), 4.38 (d, J=17.2 Hz, 1H), 4.22 (d, J=17.2 Hz, 1H), 4.12 (br d, J=4.9 Hz, 1H), 3.87 (t, J=7.5 Hz, 1H), 3.75 (dd, J=7.7, 16.0 Hz, 2H), 3.64 (d, J=7.6 Hz, 1H), 3.58 - 3.45 (m, 2H), 3.26 (br s, 1H), 3.06 - 2.82 (m, 5H), 2.64 - 2.53 (m, 2H), 2.46 - 2.21 (m, 4H), 2.15 - 1.82 (m, 7H), 1.70 (br d, J=9.1 Hz, 3H).	779.3	779.3	
A76	^{1}H NMR (400MHz, DMSO-d6) δ 11.01 (s, 1H), 9.13 (br s, 1H), 8.32 (d, *J* = 5.1 Hz, 1H), 8.17 (s, 1H), 7.30 (d, *J* = 5.1 Hz, 1H), 7.19 - 7.07 (m, 3H), 6.82 (br d, *J* = 6.4 Hz, 2H), 6.68 - 6.58 (m, 2H), 6.56 - 6.44 (m, 3H), 6.20 (d, *J* = 8.6 Hz, 2H), 5.14 (br dd, *J* = 5.0, 13.2 Hz, 2H), 4.49 - 4.39 (m, 1H), 4.33 - 4.24 (m, 1H), 4.12 (br d, *J* = 4.8 Hz, 1H), 3.85 (br t, *J* = 7.8 Hz, 1H), 3.21 (br s, 2H), 3.08 - 2.85 (m, 6H), 2.77 - 2.53 (m, 4H), 2.49 - 2.40 (m, 2H), 2.36 - 2.17 (m, 4H), 2.14 - 2.06 (m, 1H), 2.04 - 1.84 (m, 4H), 1.75 - 1.49 (m, 7H), 1.31 (br dd, *J* = 8.1, 12.3 Hz, 1H)	807.4	807.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
A77	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (br dd, *J*=12.44, 8.19 Hz, 1 H) 1.54 - 1.77 (m, 7 H) 1.85 - 2.13 (m, 7 H) 2.30 - 2.44 (m, 3 H) 2.75 - 3.15 (m, 10 H) 3.21 - 3.58 (m, 6 H) 3.87 (t, *J*=7.69 Hz, 1 H) 4.13 (d, *J*=4.88 Hz, 1 H) 4.16 - 4.27 (m, 1 H) 4.34 (d, *J*=17.01 Hz, 1 H) 4.42 - 4.51 (m, 2 H) 5.08 (dd, *J*=13.19, 5.07 Hz, 1 H) 6.21 (d, *J*=8.63 Hz, 2 H) 6.47 - 6.57 (m, 3 H) 6.59 - 6.68 (m, 2 H) 6.83 (br d, *J*=6.50 Hz, 2 H) 7.01 (s, 1 H) 7.09 - 7.18 (m, 3 H) 7.46 (s, 1 H) 8.15 (s, 1 H) 9.09 (br s, 1 H) 10.89 - 11.04 (m, 1 H)	807.4	807.4	
A78	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.94 (s, 1H), 9.07 (s, 1H), 7.19 – 7.07 (m, 4H), 7.01 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 6.8 Hz, 2H), 6.66 – 6.56 (m, 2H), 6.50 – 6.44 (m, 1H), 6.17 (d, J = 8.4 Hz, 2H), 6.05 (d, J = 8.4 Hz, 2H), 5.03 (dd, J = 13.4, 4.9 Hz, 1H), 4.40 – 4.21 (m, 3H), 4.15 – 4.06 (m, 2H), 4.01 – 3.75 (m, 4H), 3.50 – 3.39 (m, 4H), 3.20 – 3.06 (m, 2H), 3.02 – 2.84 (m, 5H), 2.79 – 2.54 (m, 2H), 2.39 – 2.29 (m, 3H), 2.15 – 1.88 (m, 4H), 1.77 – 1.59 (m, 4H).	768.4	768.4	
A79	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.93 (s, 1H), 8.17 (s, 1H), 7.18 – 7.10 (m, 4H), 7.01 (d, J = 8.6 Hz, 1H), 6.83 (d, J = 6.6 Hz, 2H), 6.65 – 6.57 (m, 2H), 6.53 – 6.46 (m, 3H), 6.26 (d, J = 8.6 Hz, 2H), 5.06 – 4.99 (m, 1H), 4.43 – 4.33 (m, 1H), 4.21 (d, J = 11.2 Hz, 1H), 4.10 (d, J = 12.4 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.87 – 3.75 (m, 3H), 2.92 (s, 2H), 2.80 – 2.70 (m, 3H), 2.42 – 2.35 (m, 1H), 2.09 – 1.89 (m, 3H), 1.74 – 1.59 (m, 2H), 1.24 (s, 2H).	754.4	754.4	
A80	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.97 (s, 1H), 8.36 (s, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.21 – 7.08 (m, 4H), 6.83 (d, J = 7.0 Hz, 3H), 6.67 – 6.59 (m, 3H), 6.53 – 6.44 (m, 4H), 6.26 (d, J = 8.6 Hz, 3H), 5.14 – 5.03 (m, 1H), 4.54 – 4.46 (m, 2H), 4.37 (d, J = 12.0 Hz, 1H), 4.23 – 4.08 (m, 3H), 2.99 – 2.90 (m, 4H), 2.64 (d, J = 14.2 Hz, 4H), 2.10 – 1.92 (m, 5H), 1.81 (d, J = 12.0 Hz, 2H), 1.73 – 1.62 (m, 4H).	753.4	753.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
A81	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.97 (s, 1H), 8.19 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.15 – 7.04 (m, 3H), 6.84 – 6.75 (m, 2H), 6.65 – 6.56 (m, 2H), 6.52 – 6.39 (m, 3H), 6.18 (d, J = 8.4 Hz, 2H), 5.12 – 5.04 (m, 1H), 4.54 – 4.44 (m, 2H), 4.41 – 4.31 (m, 1H), 4.24 – 4.16 (m, 1H), 4.08 (d, J = 4.8 Hz, 1H), 3.84 (s, 2H), 3.55 – 3.48 (m, 4H), 3.27 – 3.14 (m, 2H), 2.96 – 2.85 (m, 3H), 2.69 – 2.55 (m, 3H), 2.45 – 2.30 (m, 1H), 2.19 – 2.04 (m, 5H), 2.00 – 1.93 (m, 1H), 1.87 (d, J = 8.6 Hz, 3H), 1.69 – 1.57 (m, 3H), 1.49 – 1.37 (m, 1H), 1.29 – 1.17 (m, 2H).	793.4	793.4	
A82	^{1}H NMR (400M Hz, DMSO-d_6) δ 10.92 (s, 1H), 9.04 (S, 1H), 7.17 – 7.11 (m, 4H), 6.99 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 7.2 Hz, 2H), 6.63 – 6.50 (m, 5H), 6.20 (d, J = 8.4 Hz, 2H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.29 (dd, J = 29.6, 13.6 Hz, 2H), 4.15 – 3.91 (m, 4H), 3.78 (d, J = 11.6 Hz, 1H), 3.20 (M, 4H), 3.12 (s, 3H), 2.88 (M, 6H), 2.59 (M, 1H), 2.42 – 2.30 (m, 4H), 2.10 (M, 1H), 1.95 (M, 2H), 1.68 (M, 6H).	782.5	782.5	
A83	1HNMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.10 (s, 1H), 7.21 – 7.08 (m, 4H), 7.00 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 5.4 Hz, 2H), 6.69 – 6.58 (m, 2H), 6.50 (t, J = 8.0 Hz, 3H), 6.20 (d, J = 8.2 Hz, 2H), 5.08 – 4.99 (m, 1H), 4.31 – 4.19 (m, 2H), 4.16 – 4.06 (m, 2H), 3.96 – 3.88 (m, 1H), 3.88 – 3.74 (m, 3H), 3.52 (s, 4H), 3.19 – 3.07 (m, 1H), 3.05 – 2.88 (m, 3H), 2.77 – 2.65 (m, 3H), 2.63 – 2.55 (m, 1H), 2.44 – 2.31 (m, 1H), 2.23 – 2.06 (m, 5H), 2.03 – 1.88 (m, 2H), 1.78 – 1.63 (m, 2H), 1.54 – 1.42 (m, 1H), 1.28 – 1.15 (m, 3H).	794.8	794.8	
A84	1H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 8.16 (s, 1H), 7.07 (d, J = 6.9 Hz, 3H), 6.98 (t, J = 8.8 Hz, 1H), 6.73 (d, J = 8.1 Hz, 2H), 6.57 – 6.54 (m, 2H), 6.44 (dd, J = 12.2, 6.1 Hz, 3H), 6.36 (d, J = 8.5 Hz, 1H), 6.32 – 6.27 (m, 1H), 6.11 (s, 1H), 5.99 (d, J = 7.6 Hz, 1H), 4.64 (d, J = 4.9 Hz, 1H), 4.29 (q, J = 12.2 Hz,	731.4	731.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	1H), 3.55 (dd, J = 15.6, 9.2 Hz, 2H), 3.21 (dd, J = 17.2, 5.9 Hz, 2H), 2.94 (s, 3H), 2.89 (d, J = 7.2 Hz, 1H), 2.75 – 2.67 (m, 1H), 2.61 – 2.54 (m, 4H), 2.19 (d, J = 6.8 Hz, 3H), 2.08 (dd, J = 13.9, 7.1 Hz, 1H), 1.96 (d, J = 15.9 Hz, 2H), 1.91 – 1.84 (m, 1H), 1.75 (dd, J = 13.7, 6.9 Hz, 2H), 1.62 (dd, J = 16.6, 8.9 Hz, 6H), 1.26 – 1.15 (m, 4H).			
A85	1H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 8.18 (s, 1H), 7.07 (d, J = 7.0 Hz, 3H), 6.99 (t, J = 8.8 Hz, 1H), 6.73 (d, J = 7.7 Hz, 2H), 6.55 (d, J = 8.6 Hz, 2H), 6.46 – 6.41 (m, 3H), 6.36 (d, J = 8.4 Hz, 1H), 6.30 (dd, J = 8.7, 1.8 Hz, 1H), 6.11 (d, J = 1.8 Hz, 1H), 5.99 (d, J = 7.8 Hz, 1H), 4.64 (d, J = 5.0 Hz, 1H), 4.36 – 4.26 (m, 1H), 3.60 – 3.45 (m, 3H), 3.24 – 3.17 (m, 2H), 2.94 (s, 3H), 2.87 (s, 1H), 2.74 – 2.67 (m, 1H), 2.59 – 2.53 (m, 4H), 2.37 (d, J = 36.9 Hz, 1H), 2.17 (d, J = 7.3 Hz, 2H), 2.08 (dd, J = 13.8, 3.5 Hz, 1H), 1.97 (d, J = 15.2 Hz, 2H), 1.89 – 1.84 (m, 1H), 1.77 – 1.71 (m, 2H), 1.65 – 1.57 (m, 6H), 1.25 – 1.12 (m, 3H).	731.4	731.4	
A86	1H NMR (400 MHz, MeOD) δ 7.06 (d, J = 8.6 Hz, 5H), 6.77 – 6.73 (m, 4H), 6.70 (d, J = 9.6 Hz, 2H), 6.64 (d, J = 2.5 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 6.54 – 6.47 (m, 2H), 4.27 (dd, J = 11.8, 4.8 Hz, 1H), 3.69 (t, J = 14.9 Hz, 4H), 3.22 (d, J = 13.2 Hz, 2H), 3.13 (dd, J = 13.4, 5.1 Hz, 4H), 3.09 (s, 3H), 3.05 – 2.95 (m, 2H), 2.84 – 2.68 (m, 3H), 2.36 – 2.20 (m, 3H), 2.07 (d, J = 12.7 Hz, 4H), 2.01 – 1.87 (m, 3H), 1.75 – 1.62 (m, 3H), 1.29 (s, 2H).	713.4	713.4	
A87	1H NMR (400 MHz, MeOD) δ 7.07 – 7.02 (m, 5H), 6.73 (t, J = 7.1 Hz, 4H), 6.61 (dd, J = 5.3, 3.0 Hz, 2H), 6.49 (dd, J = 13.2, 5.3 Hz, 2H), 6.41 (dd, J = 8.5, 2.3 Hz, 1H), 6.18 (d, J = 1.9 Hz, 1H), 4.76 (d, J = 5.4 Hz, 1H), 4.27 (dd, J = 11.2, 4.3 Hz, 1H), 3.62 (d, J = 12.6 Hz, 4H), 3.29 – 3.19 (m, 2H), 3.16 – 3.03 (m, 2H), 3.01 (s, 3H), 2.98 (d, J = 5.2 Hz, 2H), 2.77 (dd, J = 11.1, 5.8 Hz, 2H), 2.67 (d, J = 13.1 Hz, 2H), 2.36 – 2.27 (m, 2H), 2.03 –	713.4	713.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	1.86 (m, 7H), 1.69 – 1.61 (m, 1H), 1.51 – 1.41 (m, 2H), 1.31 (s, 3H).			
A88	1H NMR (400 MHz, MeOD) δ 7.12 (d, J = 8.6 Hz, 2H), 7.03 (dd, J = 5.1, 1.8 Hz, 3H), 6.72 (dd, J = 8.7, 6.3 Hz, 4H), 6.64 – 6.59 (m, 2H), 6.51 – 6.46 (m, 2H), 6.40 (dd, J = 8.4, 2.3 Hz, 1H), 6.18 (d, J = 2.2 Hz, 1H), 4.76 (d, J = 5.3 Hz, 1H), 4.28 (dd, J = 11.9, 4.9 Hz, 1H), 3.56 (d, J = 12.2 Hz, 2H), 3.21 (dt, J = 13.4, 8.6 Hz, 2H), 3.00 (s, 3H), 2.96 (dd, J = 11.4, 5.9 Hz, 2H), 2.84 – 2.76 (m, 1H), 2.74 – 2.65 (m, 2H), 2.60 (dd, J = 9.2, 2.6 Hz, 2H), 2.41 – 2.17 (m, 6H), 2.04 – 1.94 (m, 2H), 1.88 (dd, J = 21.4, 9.0 Hz, 2H), 1.66 (dt, J = 17.7, 11.4 Hz, 2H), 1.32 (dd, J = 16.9, 6.0 Hz, 4H).	761.4	761.4	
A89	1H NMR (400 MHz, MeOD) δ 7.19 (d, J = 8.5 Hz, 2H), 7.05 (dd, J = 5.0, 1.7 Hz, 3H), 6.74 (dd, J = 9.2, 5.2 Hz, 4H), 6.64 (dd, J = 9.2, 2.1 Hz, 3H), 6.59 (d, J = 8.4 Hz, 1H), 6.49 (dd, J = 8.2, 2.5 Hz, 1H), 6.42 (d, J = 4.4 Hz, 1H), 4.82 (d, J = 6.0 Hz, 2H), 4.35 – 4.27 (m, 1H), 3.65 (d, J = 13.1 Hz, 2H), 3.19 – 3.09 (m, 4H), 3.07 (s, 3H), 2.98 (dd, J = 12.7, 6.6 Hz, 3H), 2.82 – 2.71 (m, 2H), 2.61 (dd, J = 18.2, 8.0 Hz, 1H), 2.45 – 2.27 (m, 4H), 2.20 – 2.14 (m, 1H), 2.03 – 1.91 (m, 3H), 1.68 – 1.58 (m, 3H), 1.30 (d, J = 8.1 Hz, 3H).	761.4	761.4	
A90	1H NMR (400 MHz, DMSO) δ 10.79 (s, 1H), 9.07 (s, 1H), 7.09 (t, J = 16.3 Hz, 5H), 6.70 (dd, J = 26.6, 5.6 Hz, 4H), 6.60 – 6.53 (m, 2H), 6.45 (d, J = 9.4 Hz, 1H), 6.34 (dd, J = 24.7, 8.3 Hz, 2H), 6.12 (s, 1H), 6.02 – 5.87 (m, 1H), 4.65 (d, J = 5.1 Hz, 1H), 4.33 (d, J = 12.9 Hz, 1H), 4.02 (t, J = 19.2 Hz, 1H), 3.59 (t, J = 12.6 Hz, 2H), 3.22 (d, J = 12.7 Hz, 2H), 3.13 – 3.05 (m, 3H), 2.95 (s, 3H), 2.87 (d, J = 6.7 Hz, 1H), 2.78 – 2.60 (m, 4H), 2.35 – 2.24 (m, 3H), 2.20 (dd, J = 12.5, 8.7 Hz, 2H), 2.14 – 2.04 (m, 2H), 1.97 – 1.86 (m, 2H), 1.82 – 1.74 (m, 2H), 1.59 (d, J = 9.4 Hz, 1H), 1.33 – 1.24 (m, 2H).	761.4	761.4	
A91	1H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.34 (s, 1H), 7.11 – 7.02 (m, 4H), 6.93 (s,	800.4	800.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	1H), 6.76 (d, J = 7.8 Hz, 2H), 6.60 – 6.52 (m, 2H), 6.50 – 6.43 (m, 1H), 6.22 – 6.14 (m, 2H), 5.09 – 4.98 (m, 1H), 4.67 (d, J = 5.0 Hz, 1H), 4.33 – 4.15 (m, 3H), 3.93 – 3.81 (m, 2H), 3.29 – 3.22 (m, 4H), 2.98 – 2.88 (m, 8H), 2.80 – 2.72 (m, 1H), 2.64 – 2.56 (m, 3H), 2.38 – 2.25 (m, 2H), 2.23 – 2.05 (m, 4H), 1.98 – 1.92 (m, 1H), 1.77 – 1.60 (m, 4H), 1.29 – 1.20 (m, 2H).			
A92	1H NMR (400 MHz, DMSO) δ 10.79 (s, 1H), 9.06 (s, 1H), 7.16 (d, J = 7.9 Hz, 2H), 7.07 (d, J = 6.6 Hz, 3H), 6.76 – 6.70 (m, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.56 (dd, J = 10.3, 5.2 Hz, 2H), 6.45 (dd, J = 9.3, 3.2 Hz, 1H), 6.41 – 6.36 (m, 1H), 6.32 (dd, J = 9.4, 3.9 Hz, 1H), 6.14 (d, J = 1.2 Hz, 1H), 5.95 (d, J = 7.3 Hz, 1H), 4.66 (t, J = 4.4 Hz, 1H), 4.38 – 4.28 (m, 1H), 4.03 (t, J = 11.8 Hz, 1H), 3.67 – 3.50 (m, 3H), 3.25 – 3.16 (m, 2H), 3.14 – 3.00 (m, 3H), 2.95 (s, 3H), 2.93 – 2.78 (m, 2H), 2.78 – 2.64 (m, 3H), 2.63 – 2.56 (m, 3H), 2.24 – 2.06 (m, 3H), 1.99 – 1.85 (m, 2H), 1.83 – 1.74 (m, 2H), 1.64 – 1.56 (m, 1H), 1.27 (dd, J = 19.9, 7.8 Hz, 2H).	761.4	761.4	
A93	1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.20 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.13 – 7.05 (m, 3H), 6.76 (d, J = 6.2 Hz, 2H), 6.62 – 6.54 (m, 2H), 6.49 – 6.44 (m, 1H), 6.23 – 6.15 (m, 2H), 5.12 – 4.98 (m, 1H), 4.67 (d, J = 5.4 Hz, 1H), 4.51 (t, J = 10.0 Hz, 2H), 4.40 – 4.33 (m, 1H), 4.26 – 4.16 (m, 1H), 3.00 – 2.81 (m, 9H), 2.68 – 2.54 (m, 3H), 2.47 – 2.31 (m, 2H), 2.24 – 2.14 (m, 3H), 2.05 – 1.88 (m, 5H), 1.82 – 1.74 (m, 2H), 1.70 – 1.54 (m, 4H), 1.31 – 1.17 (m, 2H).	799.4	799.4	
A94	1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.50 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 6.6 Hz, 3H), 6.76 (d, J = 6.2 Hz, 2H), 6.61 – 6.53 (m, 2H), 6.49 (d, J = 8.2 Hz, 1H), 6.25 – 6.13 (m, 2H), 4.81 – 4.63 (m, 2H), 4.44 (d, J = 8.4 Hz, 1H), 4.13 – 3.98 (m, 1H), 3.84 – 3.76 (m, 1H), 3.26 – 3.20 (m, 4H), 2.99 – 2.93 (m,	789.4	789.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	6H), 2.81 – 2.72 (m, 2H), 2.65 – 2.54 (m, 2H), 2.30 – 2.07 (m, 6H), 2.02 – 1.95 (m, 1H), 1.83 – 1.59 (m, 6H), 1.32 – 1.18 (m, 3H).			
A95	^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.05 (s, 1H), 8.14 (s, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 6.8 Hz, 3H), 6.85 – 6.69 (m, 2H), 6.63 – 6.53 (m, 2H), 6.45 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 6.30 (d, *J* = 10.0 Hz, 1H), 6.11 (s, 1H), 5.08 (dd, *J* = 13.2, 5.0 Hz, 1H), 4.64 (d, *J* = 5.1 Hz, 1H), 4.55 (s, 2H), 4.38 (d, *J* = 17.2 Hz, 1H), 4.21 (d, *J* = 17.0 Hz, 1H), 3.20 (dd, *J* = 12.7, 4.5 Hz, 3H), 3.00 (s, 4H), 2.94 (s, 4H), 2.92 (s, 3H), 2.84 (s, 1H), 2.67 (s, 1H), 2.62 (s, 1H), 2.57 (s, 1H), 2.43 (d, *J* = 4.8 Hz, 1H), 2.41 – 2.37 (m, 1H), 2.34 (d, *J* = 14.2 Hz, 1H), 1.97 (d, *J* = 11.6 Hz, 6H), 1.79 – 1.69 (m, 2H), 1.65 (s, 2H), 1.59 (s, 1H), 1.53 (s, 1H), 1.50 – 1.37 (m, 2H)	821.4	821.9	
A96	1H NMR (400M Hz, DMSO-*d*6) δ 7.08-7.02 (m, 5H), 6.79-6.74 (m, 4H), 6.72-6.70 (m, 2H), 6.63 (s, 1H), 6.59-6.57 (m, 1H), 6.49-6.47 (m, 2H), 4.28-4.24 (m, 1H), 3.58-3.55 (m, 2H), 3.48-3.46 (m, 1H), 3.26-3.24 (m, 4H), 3.13-3.12 (m, 2H), 3.08-3.06 (m, 3H), 3.05-2.99 (m, 3H), 2.81-2.73 (m, 4H), 2.32-2.22 (m, 4H), 2.07-2.00 (m, 2H), 1.95-1.87 (m, 4H), 1.85-1.76 (m, 4H), 1.72-1.66 (m, 4H)	753.4	753.4	
A97	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.14 – 7.07 (m, 3H), 7.01 (d, J = 8.6 Hz, 1H), 6.87 – 6.81 (m, 2H), 6.69 – 6.58 (m, 2H), 6.55 – 6.47 (m, 1H), 6.26 (d, J = 12.0 Hz, 1H), 6.06 (d, J = 7.0 Hz, 1H), 5.07 – 4.98 (m, 1H), 4.45 (d, J = 5.2 Hz, 1H), 4.40 – 4.33 (m, 1H), 4.30 – 4.22 (m, 1H), 4.14 – 4.07 (m, 1H), 4.02 – 3.94 (m, 1H), 3.86 – 3.78 (m, 1H), 3.47 (s, 3H), 3.28 – 3.16 (m, 4H), 3.04 – 2.88 (m, 5H), 2.77 – 2.65 (m, 1H), 2.62 – 2.55 (m, 1H), 2.46 – 2.28 (m, 4H), 2.27 – 2.16 (m, 3H), 2.14 – 2.05 (m, 1H), 1.98 – 1.92 (m, 1H), 1.80 –	800.4	800.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	1.69 (m, 4H), 1.65 – 1.56 (m, 1H), 1.29 – 1.14 (m, 2H)..			
A98	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.13 – 7.07 (m, 3H), 7.04 – 6.98 (m, 1H), 6.91 – 6.82 (m, 2H), 6.67 – 6.58 (m, 2H), 6.53 – 6.46 (m, 1H), 6.29 – 6.22 (m, 1H), 6.06 (d, J = 7.0 Hz, 1H), 5.08 – 4.98 (m, 1H), 4.45 (d, J = 5.2 Hz, 1H), 4.40 – 4.33 (m, 1H), 4.29 – 4.21 (m, 1H), 4.16 – 4.05 (m, 1H), 4.00 – 3.94 (m, 1H), 3.86 – 3.76 (m, 1H), 3.47 (s, 3H), 3.36 – 3.28 (m, 4H), 3.04 – 2.81 (m, 6H), 2.77 – 2.66 (m, 1H), 2.61 – 2.54 (m, 1H), 2.46 – 2.33 (m, 3H), 2.28 – 2.16 (m, 3H), 2.13 – 2.06 (m, 1H), 1.98 – 1.91 (m, 1H), 1.80 – 1.69 (m, 4H), 1.64 – 1.52 (m, 1H), 1.28 – 1.13 (m, 2H).	800.4	800.4	
A99	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.21 – 6.98 (m, 5H), 6.75 (d, J = 6.4 Hz, 2H), 6.63 – 6.45 (m, 3H), 6.18 (dd, J = 10.4, 6.8 Hz, 2H), 5.03 (dd, J = 13.2, 4.8 Hz, 1H), 4.67 (d, J = 4.8 Hz, 1H), 4.30 (dd, J = 34.4, 13.6 Hz, 2H), 4.10 (d, J = 16.8 Hz, 1H), 3.95 (dd, J = 8.4, 6.8 Hz, 1H), 3.80 (d, J = 11.2 Hz, 1H), 3.25 – 3.03 (m, 4H), 2.95 (s, 3H), 2.92 – 2.69 (m, 9H), 2.57 (d, J = 16.8 Hz, 1H), 2.43 – 1.92 (m, 8H), 1.77 – 1.40 (m, 8H).	840.4	840.4	
A100	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1 H), 9.13 (br s, 1 H), 7.22 - 7.43 (m, 2 H), 7.00 - 7.15 (m, 3 H), 6.68 - 6.81 (m, 2 H), 6.41 - 6.62 (m, 3 H), 6.11 - 6.24 (m, 2 H), 5.08 (dd, *J* = 13.32, 4.94 Hz, 1 H), 4.66 (br d, *J* = 5.00 Hz, 1 H), 4.52 (s, 2 H), 4.35 - 4.36 (m, 1 H), 4.37 (d, *J* = 17.13 Hz, 1 H), 4.21 (d, *J* = 17.13 Hz, 1 H), 3.24 (br s, 1 H), 2.72 - 2.95 (m, 12 H), 2.55 - 2.64 (m, 2 H), 2.32 - 2.46 (m, 2 H), 2.05 - 2.21 (m, 3 H), 1.83 - 2.03 (m, 6 H), 1.51 - 1.77 (m, 7 H), 1.44 (br dd, *J* = 9.26, 5.63 Hz, 2 H).	839.4	839.4	
A101	1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.20 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.11 – 7.07 (m, 3H), 6.77 (d, J = 7.2 Hz, 2H), 6.59 – 6.46 (m, 3H), 6.22-6.18 (m, 2H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H),	840.4	840.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	4.67 (d, J = 5.6 Hz, 1H), 4.55-4.50 (m, 2H), 4.09-4.06 (m, 1H), 4.29(dd, J = 68.4, 17.2 Hz, 2H), 3.23-2.82 (m, 9H), 2.67-2.53 (m, 3H), 2.44 – 2.14 (m, 5H), 2.00 – 1.62 (m, 11H), 1.25 – 1.22 (m, 2H).			
A102	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.14 (s, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.13 – 7.05 (m, 3H), 7.00 (d, J = 8.4 Hz, 1H), 6.88 – 6.78 (m, 2H), 6.68 – 6.58 (m, 2H), 6.54 – 6.45 (m, 1H), 6.24 (d, J = 11.6Hz, 1H), 6.05 (d, J = 7.2 Hz, 1H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.44 (d, J = 5.2 Hz, 1H), 4.38 – 4.31 (m, 1H), 4.26 (d, J = 16.8 Hz, 1H), 4.10 (d, J = 16.8 Hz, 1H), 4.00 – 3.90 (m, 1H), 3.80 (d, J = 11.6 Hz, 1H), 3.34 – 3.31 (m, 1H), 3.18 – 3.11 (m, 1H), 3.06 – 2.54 (m, 12H), 2.47 – 2.36 (m, 3H), 2.28 – 2.07 (m, 2H), 2.00 – 1.87 (m, 3H), 1.73 (t, J = 10.4 Hz, 2H), 1.68 – 1.60 (m, 2H), 1.57 – 1.48 (m, 2H), 1.46 – 1.35 (m, 2H).	840.4	840.4	
A103	1H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.13 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.13 – 7.05 (m, 3H), 7.00 (d, J = 8.4 Hz, 1H), 6.88 – 6.77 (m, 2H), 6.68 – 6.57 (m, 2H), 6.49 (dd, J = 8.2, 2.4 Hz, 1H), 6.24 (d, J = 11.6 Hz, 1H), 6.05 (d, J = 7.2 Hz, 1H), 5.03 (dd, J = 13.2, 4.8 Hz, 1H), 4.44 (d, J = 5.2 Hz, 1H), 4.34 (dd, J = 10.8, 2.4 Hz, 1H), 4.26 (d, J = 16.8 Hz, 1H), 4.09 (d, J = 16.8 Hz, 1H), 4.01 – 3.89 (m, 1H), 3.80 (d, J = 11.2 Hz, 1H), 3.47 (s, 3H), 3.19 – 3.10 (m, 1H), 3.08 – 2.52 (m, 12H), 2.48 – 2.30 (m, 4H), 2.30 – 2.17 (m, 1H), 2.16 – 2.05 (m, 1H), 2.01 – 1.87 (m, 3H), 1.79 – 1.69 (m, 2H), 1.68 – 1.59 (m, 2H), 1.57 – 1.47 (m, 2H), 1.45 – 1.33 (m, 2H).	840.4	840.4	
A104	1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.15 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.16 – 7.00 (m, 3H), 6.75 (d, J = 6.0 Hz, 2H), 6.65 – 6.42 (m, 3H), 6.26 – 6.10 (m, 2H), 4.78 – 4.61 (m, 2H), 4.43 (d, J = 8.4 Hz, 1H), 4.13 – 4.03 (m, 1H), 3.76 (d, J = 11.6 Hz, 1H), 3.30 – 3.11 (m, 4H), 3.04 – 2.93 (m, 5H), 2.92 –	829.4	829.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	2.66 (m, 10H), 2.45 – 2.33 (m, 2H), 2.21 – 2.06 (m, 3H), 2.01 – 1.89 (m, 3H), 1.79 – 1.62 (m, 4H), 1.59 – 1.53 (m, 2H), 1.48 – 1.37 (m, 2H).			
A105	^{1}H NMR (400 MHz, DMSO) δ 10.79 (s, 1H), 9.10 (d, *J* = 16.1 Hz, 2H), 7.07 (d, *J* = 6.8 Hz, 3H), 6.93 (t, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 2.9 Hz, 2H), 6.62 – 6.51 (m, 2H), 6.50 – 6.43 (m, 3H), 6.39 (s, 2H), 6.14 (d, *J* = 16.4 Hz, 1H), 4.66 (d, *J* = 5.1 Hz, 1H), 4.31 (s, 1H), 3.21 (dd, *J* = 22.7, 2.3 Hz, 4H), 3.05 (d, *J* = 4.8 Hz, 4H), 2.96 (s, 3H), 2.91 (d, *J* = 11.8 Hz, 2H), 2.82 – 2.66 (m, 3H), 2.54 (s, 3H), 2.35 – 2.31 (m, 1H), 2.18 – 1.99 (m, 4H), 1.93 – 1.81 (m, 5H), 1.71 (s, 2H), 1.65 – 1.53 (m, 5H)	771.4	771.4	
A106	^{1}H NMR (400 MHz, DMSO) δ 10.80 (s, 1H), 9.07 (s, 2H), 7.07 (d, *J* = 6.6 Hz, 3H), 6.93 (t, *J* = 8.7 Hz, 1H), 6.72 (d, *J* = 5.9 Hz, 2H), 6.53 (dd, *J* = 19.7, 11.2 Hz, 3H), 6.49 – 6.42 (m, 3H), 6.39 (s, 1H), 6.22 – 6.04 (m, 1H), 4.65 (d, *J* = 5.2 Hz, 1H), 4.31 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.25 – 3.15 (m, 4H), 3.05 (dd, *J* = 12.3, 6.2 Hz, 4H), 2.95 (s, 3H), 2.91 – 2.83 (m, 2H), 2.80 – 2.67 (m, 3H), 2.63 – 2.53 (m, 3H), 2.33 (s, 1H), 2.04 (dd, *J* = 11.7, 7.7 Hz, 4H), 1.94 – 1.77 (m, 5H), 1.75 – 1.67 (m, 2H), 1.63 – 1.51 (m, 5H)	771.4	771.4	
A107	1H NMR (400M Hz, DMSO-*d6*) δ 10.83 (s, 1H), 9.88 (brs, 1H), 9.06 (s, 1H), 8.54 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.49-7.46 (m, 1H), 7.09-7.05 (m, 3H), 6.73-6.71 (m, 2H), 6.57-6.55 (m, 2H), 6.52 (s, 1H), 6.39-6.32 (m, 2H), 6.13-6.12 (m, 1H), 4.76-4.69 (m, 1H), 4.65 (d, *J* = 4.0 Hz, 1H), 4.50 (d, *J* = 10.4 Hz, 1H), 4.22-4.14 (m, 2H), 3.33-3.20 (m, 6H), 3.13-3.10 (m, 2H), 3.06-3.02 (m, 4H), 2.94 (s, 3H), 2.79-2.73 (m, 2H), 2.69-2.67 (m, 1H), 2.22-2.14 (m, 3H), 2.05-1.96 (m, 3H), 1.71-1.67 (m, 2H), 1.59-1.54 (m, 6H)	811.4	811.4	
A108	1H NMR (400 MHz, MeOD) δ 10.84 (s, 1H), 9.94 (brs, 1H), 9.06 (brs, 1H), 8.55 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 6.4 Hz, 1H), 7.11-7.05 (m, 4H), 6.72	811.4	811.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	(d, J =7.8 Hz, 2H), 6.58-6.53 (m, 2H), 6.52 (s, 1H), 6.46-6.43 (m, 1H), 6.17-6.15 (m, 1H), 4.76-4.73 (m, 1H), 4.68-4.65 (m, 1H), 4.53-4.50 (m, 1H), 4.20-4.16 (m, 2H), 3.24-3.20 (m, 4H), 3.11-3.06 (m, 2H), 2.95 (s, 3H), 2.77-2.67 (m, 1H), 2.20-2.16 (m, 2H), 2.08-1.98 (m, 4H), 1.73-1.68 (m, 2H), 1.60-1.55 (m, 6H), 1.29-1.21 (m, 8H), 0.87-0.82 (m, 1H)			
A109	^{1}H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 9.07 (s, 2H), 7.20 – 7.00 (m, 4H), 6.97 – 6.88 (m, 1H), 6.80 (d, *J* = 10.8 Hz, 2H), 6.73 (d, *J* = 7.9 Hz, 2H), 6.60 – 6.50 (m, 2H), 6.45 (d, *J* = 8.6 Hz, 1H), 6.39 (s, 1H), 6.16 (s, 1H), 5.51 (s, 1H), 4.65 (d, *J* = 5.2 Hz, 1H), 4.37 (s, 1H), 3.19 (s, 4H), 3.08 (dd, *J* = 17.8, 11.0 Hz, 3H), 2.94 – 2.85 (m, 3H), 2.67 (s, 3H), 2.59 (s, 1H), 2.33 (s, 1H), 2.22 – 2.09 (m, 1H), 2.05 (dd, *J* = 14.6, 7.5 Hz, 4H), 2.00 – 1.85 (m, 3H), 1.83 – 1.69 (m, 4H), 1.62 – 1.53 (m, 5H), 1.24 (s, 2H), 1.18 (t, *J* = 7.3 Hz, 1H)	771.4	771.5	
A110	1H NMR (400M Hz, DMSO-*d*6) δ 7.08-7.02 (m, 5H), 6.79-6.74 (m, 4H), 6.72-6.70 (m, 2H), 6.63 (s, 1H), 6.59-6.57 (m, 1H), 6.49-6.47 (m, 2H), 4.28-4.24 (m, 1H), 3.58-3.55 (m, 2H), 3.48-3.46 (m, 1H), 3.26-3.24 (m, 4H), 3.13-3.12 (m, 2H), 3.08-3.06 (m, 3H), 3.05-2.99 (m, 3H), 2.81-2.73 (m, 4H), 2.32-2.22 (m, 4H), 2.07-2.00 (m, 2H), 1.95-1.87 (m, 4H), 1.85-1.76 (m, 4H), 1.72-1.66 (m, 4H)	753.4	753.4	
A111	1H NMR (400 MHz, DMSO) δ 10.82 (s, 1H), 9.11 (s, 1H), 8.48 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.08 (M, 3H), 6.75 (d, J = 6.8 Hz, 2H), 6.62 – 6.51 (m, 2H), 6.51 – 6.45 (m, 1H), 6.26 – 6.11 (m, 2H), 4.77 – 4.63 (m, 2H), 4.43 (d, J = 10.8 Hz, 1H), 4.12 – 4.01 (m, 1H), 3.76 (d, J = 11.6 Hz, 1H), 3.27 – 3.12 (m, 3H), 3.01 – 2.92 (m, 5H), 2.92 – 2.69 (m, 9H), 2.46 – 2.36 (m, 2H), 2.22 – 2.06 (m, 3H), 2.01 – 1.90 (m, 3H), 1.75 – 1.53 (m, 6H), 1.47 – 1.38 (m, 2H).	829.4	829.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
A112	^{1}H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 9.16 (s, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.18 (dd, *J* = 13.0, 5.7 Hz, 3H), 7.11 (s, 1H), 7.02 (s, 1H), 6.90 (d, *J* = 7.2 Hz, 2H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 1.8 Hz, 1H), 6.58 – 6.45 (m, 3H), 5.04 (dd, *J* = 13.0, 5.0 Hz, 1H), 4.41 (d, *J* = 10.0 Hz, 1H), 4.28 (d, *J* = 17.0 Hz, 1H), 4.14 (dd, *J* = 11.0, 6.1 Hz, 2H), 4.06 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.52 (s, 3H), 3.41 (d, *J* = 9.9 Hz, 2H), 3.29 (s, 1H), 3.23 (s, 3H), 3.13 – 3.00 (m, 2H), 2.95 (dd, *J* = 12.8, 6.0 Hz, 2H), 2.88 (dd, *J* = 17.6, 5.4 Hz, 2H), 2.67 (s, 1H), 2.60 (s, 1H), 2.56 (s, 1H), 2.49 – 2.28 (m, 2H), 2.02 (dd, *J* = 11.8, 5.5 Hz, 3H), 1.96 – 1.89 (m, 1H), 1.76 (dd, *J* = 13.6, 6.1 Hz, 1H), 1.56 (s, 4H), 1.44 (s, 2H)	793.4	793.4	
A113	^{1}H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 9.20 (s, 1H), 7.23 (dd, *J* = 17.6, 6.2 Hz, 3H), 7.17 (d, *J* = 15.6 Hz, 3H), 7.02 (d, *J* = 51.1 Hz, 2H), 6.93 (d, *J* = 7.0 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 1H), 6.62 (s, 1H), 6.51 (d, *J* = 9.1 Hz, 1H), 5.04 (dd, *J* = 13.1, 5.1 Hz, 1H), 4.42 (d, *J* = 10.3 Hz, 1H), 4.30 (s, 1H), 4.25 (s, 1H), 4.18 (d, *J* = 15.1 Hz, 3H), 4.13 – 4.02 (m, 2H), 3.27 (s, 4H), 3.17 (d, *J* = 13.8 Hz, 1H), 3.08 (d, *J* = 10.0 Hz, 2H), 3.02 (d, *J* = 3.9 Hz, 1H), 3.00 – 2.75 (m, 5H), 2.72 (dd, *J* = 12.0, 3.4 Hz, 1H), 2.67 (s, 1H), 2.60 (s, 1H), 2.41 (dd, *J* = 12.7, 2.5 Hz, 1H), 1.99 (dd, *J* = 28.3, 8.8 Hz, 5H), 1.78 (d, *J* = 13.5 Hz, 1H), 1.59 (d, *J* = 6.5 Hz, 4H), 1.46 (s, 2H), 1.19 (dd, *J* = 19.1, 11.5 Hz, 1H)	793.4	793.4	
A114	1H NMR (400 MHz, MeOD) δ 10.83 (s, 1H), 9.15 (s, 1H), 8.55 (d, J = 12.0 Hz, 1H), 7.62 (d, J =8.0 Hz, 1H), 7.43 (brs, 1H), 7.20-7.13 (m, 3H), 7.02 (s, 1H), 6.89 (d, J =6.8 Hz, 2H), 6.65 (d, J =7.6 Hz, 1H), 6.61 (s, 1H), 6.52-6.48 (m, 3H), 4.75-4.68 (m, 1H), 4.50-4.46 (m, 1H), 4.19-4.12 (m, 2H), 3.60-3.49 (m, 2H), 3.24-3.22 (m, 4H), 3.12-3.07 (m, 1H), 3.02-3.00 (m, 1H), 2.97-2.96 (m, 2H), 2.94-2.91 (m, 1H), 2.88-2.82 (m, 2H), 2.68-2.65 (m, 1H), 2.35-2.30 (m, 1H), 2.21-2.15 (m, 1H), 2.05-1.96 (m, 5H), 1.79-1.73 (m,	782.4	782.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	1H), 1.59-1.53 (m, 4H), 1.46-1.42 (m, 3H), 1.26-1.20 (m, 2H)			
A115	1H NMR (400M Hz, MeOD) δ 10.83 (s, 1H), 9.15 (s, 1H), 8.56-8.51 (m, 1H), 7.64-7.60 (m, 1H), 7.43 (brs, 1H), 7.20-7.13 (m, 3H), 7.02 (s, 1H), 6.89 (d, J =6.8 Hz, 2H), 6.65 (d, J =7.6 Hz, 1H), 6.61 (s, 1H), 6.52-6.48 (m, 3H), 4.75-4.68 (m, 1H), 4.50-4.46 (m, 1H), 4.19-4.12 (m, 2H), 3.60-3.49 (m, 2H), 3.24-3.22 (m, 4H), 3.12-3.07 (m, 1H), 3.02-3.00 (m, 1H), 2.97-2.96 (m, 2H), 2.94-2.91 (m, 1H), 2.88-2.82 (m, 2H), 2.68-2.65 (m, 1H), 2.35-2.30 (m, 1H), 2.21-2.15 (m, 1H), 2.05-1.96 (m, 5H), 1.79-1.73 (m, 1H), 1.59-1.53 (m, 4H), 1.46-1.42 (m, 3H), 1.26-1.20 (m, 2H)	782.4	782.5	
A116	^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 9.14 (s, 1H), 7.30 (d, *J* = 21.4 Hz, 2H), 7.13 (dd, *J* = 32.7, 21.2 Hz, 4H), 6.89 (d, *J* = 6.3 Hz, 2H), 6.72 – 6.58 (m, 2H), 6.50 (d, *J* = 9.6 Hz, 3H), 5.09 (d, *J* = 7.7 Hz, 1H), 4.64 (s, 2H), 4.39 (d, *J* = 17.4 Hz, 1H), 4.23 (d, *J* = 17.5 Hz, 1H), 4.13 (s, 1H), 3.45 (dd, *J* = 11.0, 4.3 Hz, 4H), 3.24 (s, 4H), 3.12 – 2.98 (m, 2H), 2.98 – 2.80 (m, 3H), 2.71 (dd, *J* = 18.6, 11.0 Hz, 2H), 2.60 (dd, *J* = 15.5, 4.0 Hz, 2H), 2.46 – 2.30 (m, 2H), 2.14 – 1.92 (m, 7H), 1.82 – 1.70 (m, 1H), 1.56 (s, 3H), 1.44 (dd, *J* = 6.0, 2.0 Hz, 2H)	792.4	792.5	
A117	^{1}H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 9.14 (s, 1H), 8.14 (s, 1H), 7.33 (s, 2H), 7.25 – 7.11 (m, 3H), 7.05 (s, 1H), 6.89 (d, *J* = 6.9 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 1H), 6.60 (s, 1H), 6.49 (dt, *J* = 18.3, 9.0 Hz, 3H), 5.09 (dd, *J* = 13.2, 5.3 Hz, 1H), 4.60 (s, 2H), 4.39 (d, *J* = 17.1 Hz, 1H), 4.22 (d, *J* = 17.1 Hz, 1H), 4.12 (d, *J* = 4.8 Hz, 1H), 3.23 (s, 6H), 2.94 (ddd, *J* = 28.2, 16.6, 4.1 Hz, 6H), 2.62 (t, *J* = 19.9 Hz, 3H), 2.42 (dd, *J* = 13.9, 4.2 Hz, 2H), 2.13 – 1.94 (m, 6H), 1.91 – 1.80 (m, 2H), 1.80 – 1.69 (m, 1H), 1.53 (d, *J* = 19.3 Hz, 4H), 1.44 (s, 2H)	792.4	792.5	
A118	1H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 8.31 (s, 1H), 7.09 (d, J = 6.8 Hz, 3H), 6.95 –	749.4	749.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	6.89 (m, 1H), 6.87 – 6.80 (m, 1H), 6.75 (t, J = 8.8 Hz, 3H), 6.60 – 6.53 (m, 2H), 6.50 – 6.45 (m, 1H), 6.24 – 6.15 (m, 2H), 5.38 (d, J = 6.7 Hz, 1H), 4.67 (d, J = 4.8 Hz, 1H), 4.41 – 4.32 (m, 1H), 3.30 – 3.22 (m, 4H), 2.98 – 2.90 (m, 6H), 2.80 – 2.72 (m, 1H), 2.64 – 2.56 (m, 2H), 2.39 – 2.33 (m, 1H), 2.21 – 2.14 (m, 3H), 2.09 – 1.92 (m, 4H), 1.82 – 1.68 (m, 4H), 1.65 – 1.55 (m, 4H), 1.30 – 1.19 (m, 2H).			
A119	1H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 8.23 (s, 1H), 7.12 – 7.06 (m, 3H), 6.99 (t, J = 8.8 Hz, 1H), 6.78 – 6.73 (m, 2H), 6.60 – 6.53 (m, 2H), 6.49 – 6.39 (m, 3H), 6.22 – 6.15 (m, 2H), 5.99 (d, J = 7.6 Hz, 1H), 4.67 (d, J = 5.2 Hz, 1H), 4.34 – 4.26 (m, 1H), 3.31 – 3.22 (m, 4H), 2.97 – 2.91 (m, 6H), 2.76 – 2.69 (m, 1H), 2.64 – 2.56 (m, 3H), 2.21 – 2.14 (m, 3H), 2.12 – 2.04 (m, 1H), 2.00 – 1.85 (m, 3H), 1.81 – 1.72 (m, 2H), 1.67 – 1.56 (m, 7H), 1.29 – 1.17 (m, 2H).	749.4	749.4	
A120	1H NMR (400M Hz, MeOD) δ 10.94 (s, 1H), 9.14 (s, 1H), 7.19-7.13 (m, 4H), 7.03 (s, 2H), 6.89 (d, J =7.2 Hz, 1H), 6.61 (s, 1H), 6.53-6.48 (m, 3H), 5.06–5.00 (m, 1H), 4.35-4.19 (m, 5H), 4.13-4.12 (m, 1H), 3.56-3.51 (m, 3H), 3.24-3.21 (m, 3H), 3.11-3.08 (m, 1H), 2.97-2.88 (m, 4H), 2.87-2.85 (m, 1H), 2.69-2.67 (m, 1H), 2.38-2.31 (m, 1H), 2.07-1.96 (m, 5H), 1.77-1.73 (m, 1H), 1.55 (s, 3H), 1.43 (s, 2H), 1.29-1.23 (m, 5H)	793.4	793.5	
A121	^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.21 (s, 1H), 7.23 – 7.17 (m, 4H), 7.03 (s, 1H), 6.93 (d, *J* = 6.8 Hz, 3H), 6.68 (d, *J* = 8.4 Hz, 2H), 6.62 (s, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 5.04 (dd, *J* = 13.1, 5.1 Hz, 1H), 4.34 (d, *J* = 11.7 Hz, 1H), 4.18 (d, *J* = 16.4 Hz, 3H), 4.07 – 3.95 (m, 2H), 3.38 (s, 5H), 3.29 (s, 3H), 3.09 (s, 2H), 2.98 – 2.85 (m, 4H), 2.75 – 2.59 (m, 3H), 2.40 – 2.30 (m, 1H), 2.05 – 1.92 (m, 4H), 1.80 (s, 1H), 1.59 (d, *J* = 6.9 Hz, 4H), 1.47 (s, 2H)	793.4	793.5	
A122	1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.32 (s, 1H), 7.46 (s, 1H), 7.14 – 7.06 (m,	799.4	799.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	3H), 6.99 (d, J = 9.6 Hz, 1H), 6.76 (d, J = 6.2 Hz, 2H), 6.62 – 6.53 (m, 2H), 6.50 – 6.42 (m, 1H), 6.23 – 6.15 (m, 2H), 5.12 – 5.03 (m, 1H), 4.67 (d, J = 5.2 Hz, 1H), 4.50 – 4.44 (m, 2H), 4.36 – 4.30 (m, 1H), 4.24 – 4.18 (m, 1H), 3.29 – 3.19 (m, 4H), 2.97 – 2.82 (m, 8H), 2.62 – 2.54 (m, 2H), 2.42 – 2.34 (m, 1H), 2.23 – 2.14 (m, 3H), 2.01 – 1.88 (m, 5H), 1.81 – 1.74 (m, 2H), 1.70 – 1.59 (m, 4H), 1.30 – 1.18 (m, 2H).			
A123	^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.13 (s, 1H), 7.25 – 7.11 (m, 4H), 7.09 – 6.85 (m, 4H), 6.75 – 6.42 (m, 4H), 6.00 (d, *J* = 8.6 Hz, 1H), 5.12 – 4.91 (m, 1H), 4.47 – 3.74 (m, 7H), 2.99 – 2.86 (m, 5H), 2.80 – 2.54 (m, 3H), 2.47 – 2.36 (m, 1H), 2.20 – 1.94 (m, 5H), 1.87 – 1.62 (m, 6H), 1.57 – 1.38 (m, 3H), 0.98 – 0.84 (m, 2H).	793.4	793.4	
A124	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.35 (s, 1H), 7.26 – 7.08 (m, 3H), 7.06 – 6.85 (m, 5H), 6.68 – 6.48 (m, 4H), 6.00 (d, *J* = 8.6 Hz, 1H), 5.08 – 4.97 (m, 1H), 4.32 – 4.15 (m, 3H), 3.95 – 3.77 (m, 3H), 3.55 – 3.45 (m, 4H), 3.33 – 3.14 (m, 3H), 2.92 (d, *J* = 11.4 Hz, 4H), 2.16 – 1.94 (m, 6H), 1.85 – 1.66 (m, 6H), 1.42 (t, *J* = 12.4 Hz, 3H), 1.24 (s, 2H), 0.97 – 0.86 (m, 2H).	793.4	793.4	
A125	^{1}H NMR (400 MHz, MeOD) δ 7.38 (s, 1H), 7.14 (dd, *J* = 14.2, 5.6 Hz, 4H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 6.8 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.64 (dd, *J* = 8.3, 2.3 Hz, 2H), 6.55 (s, 1H), 6.49 (d, *J* = 8.8 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.56 (s, 2H), 4.39 (t, *J* = 12.0 Hz, 2H), 4.17 (d, *J* = 4.7 Hz, 1H), 3.35 (dd, *J* = 11.8, 5.4 Hz, 5H), 3.25 (d, *J* = 7.6 Hz, 3H), 3.03 (d, *J* = 6.8 Hz, 4H), 2.88 (dd, *J* = 19.0, 5.9 Hz, 2H), 2.77 (d, *J* = 13.6 Hz, 3H), 2.68 (d, *J* = 11.4 Hz, 1H), 2.47 (dd, *J* = 13.5, 4.7 Hz, 1H), 2.14 (t, *J* = 12.1 Hz, 7H), 1.97 (d, *J* = 14.7 Hz, 2H), 1.85 (d, *J* = 5.3 Hz, 1H), 1.70 (s, 2H), 1.62 (t, *J* = 9.0 Hz, 2H), 1.56 (d, *J* = 3.8 Hz, 2H)	792.4	792.4	
A126	^{1}H NMR (400 MHz, MeOD) δ 7.39 (s, 1H), 7.20 – 7.10 (m, 4H), 7.06 (d, *J* = 2.2 Hz, 1H),	792.4	792.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	6.88 (d, *J* = 6.9 Hz, 2H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 6.6 Hz, 2H), 6.58 – 6.51 (m, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.57 (s, 4H), 4.47 – 4.32 (m, 2H), 4.17 (d, *J* = 4.8 Hz, 1H), 3.34 (s, 6H), 3.28 – 3.23 (m, 3H), 3.04 (dd, *J* = 12.8, 5.6 Hz, 4H), 2.96 – 2.82 (m, 3H), 2.82 – 2.63 (m, 3H), 2.47 (dd, *J* = 12.7, 3.8 Hz, 1H), 2.31 – 2.05 (m, 7H), 1.98 (d, *J* = 16.6 Hz, 2H), 1.82 (d, *J* = 16.1 Hz, 1H), 1.69 (s, 2H), 1.63 (t, *J* = 9.5 Hz, 2H), 1.56 (s, 2H)			
A127	1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 8.31 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.22 – 7.12 (m, 3H), 7.01 (d, J = 11.8 Hz, 1H), 6.88 (d, J = 7.2 Hz, 2H), 6.70 – 6.59 (m, 2H), 6.49 (d, J = 8.2 Hz, 2H), 6.00 (d, J = 8.4 Hz, 1H), 4.78 – 4.67 (m, 1H), 4.44 (d, J = 8.6 Hz, 1H), 4.15 – 4.04 (m, 2H), 3.77 (d, J = 10.4 Hz, 1H), 3.30 (d, J = 10.8 Hz, 3H), 3.19 (s, 1H), 2.92 (d, J = 10.6 Hz, 3H), 2.75 (d, J = 8.8 Hz, 2H), 2.19 – 1.96 (m, 7H), 1.85 – 1.65 (m, 7H), 1.42 (t, J = 11.6 Hz, 4H), 1.24 (s, 1H), 0.99 – 0.86 (m, 2H).	782.4	782.4	
A128	^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.30 (s, 1H), 7.45 (s, 1H), 7.22 – 7.13 (m, 3H), 7.00 (s, 2H), 6.88 (d, *J* = 7.2 Hz, 2H), 6.71 – 6.56 (m, 2H), 6.50 (d, *J* = 8.4 Hz, 2H), 6.00 (d, *J* = 8.6 Hz, 1H), 5.13 – 5.04 (m, 1H), 4.45 (s, 2H), 4.39 – 4.10 (m, 4H), 3.31 (d, *J* = 13.0 Hz, 5H), 3.00 – 2.79 (m, 5H), 2.10 (d, *J* = 6.6 Hz, 2H), 2.00 – 1.79 (m, 8H), 1.67 (s, 4H), 1.49 – 1.38 (m, 3H), 1.24 (s, 2H), 0.89 (d, *J* = 12.2 Hz, 2H).	792.4	792.4	
A129	1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.30 (s, 1H), 7.44 (s, 1H), 7.12 – 6.97 (m, 4H), 6.75 (d, J = 6.4 Hz, 2H), 6.60 – 6.44 (m, 3H), 6.22 – 6.12 (m, 2H), 5.07 (dd, J = 13.2, 4.8 Hz, 1H), 4.67 (d, J = 4.8 Hz, 1H), 4.45 (s, 2H), 4.36 – 4.18 (m, 2H), 3.25 (d, J = 9.2 Hz, 1H), 2.98 – 2.75 (m, 12H), 2.64 – 2.55 (m, 1H), 2.46 – 2.29 (m, 4H), 2.19 – 2.10 (m, 1H), 2.03 – 1.85 (m, 7H), 1.70 – 1.54 (m, 7H), 1.46 – 1.38 (m, 2H)	839.4	839.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
A130	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.41 (s, 1H), 7.23 – 7.13 (m, 3H), 7.07 – 6.83 (m, 5H), 6.70 – 6.47 (m, 4H), 6.00 (d, J = 8.6 Hz, 1H), 5.07 – 4.94 (m, 1H), 4.31 – 4.09 (m, 4H), 3.92 – 3.78 (m, 2H), 3.51 (s, 2H), 3.18 (s, 3H), 2.98 – 2.87 (m, 5H), 2.77 – 2.67 (m, 1H), 2.34 (d, J = 12.0 Hz, 1H), 2.12 – 1.95 (m, 6H), 1.74 (d, J = 11.4 Hz, 4H), 1.51 – 1.38 (m, 3H), 1.24 (s, 3H), 0.97 – 0.87 (m, 2H).	793.4	793.4	
A131	^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.31 (s, 2H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.31 – 7.12 (m, 4H), 6.99 (s, 1H), 6.88 (d, *J* = 7.4 Hz, 2H), 6.68 – 6.59 (m, 2H), 6.50 (d, *J* = 8.2 Hz, 2H), 6.00 (d, *J* = 8.4 Hz, 1H), 5.09 – 5.00 (m, 1H), 4.52 (d, *J* = 9.6 Hz, 2H), 4.37 (d, *J* = 11.2 Hz, 1H), 4.25 – 4.10 (m, 2H), 3.04 – 2.88 (m, 4H), 2.79 (d, *J* = 7.0 Hz, 3H), 2.12 – 2.00 (m, 3H), 1.98 (d, *J* = 6.8 Hz, 2H), 1.81 – 1.64 (m, 7H), 1.49 – 1.36 (m, 4H), 1.24 (s, 5H), 1.00 – 0.83 (m, 3H).	792.4	792.4	
A132	1H NMR (400 MHz, DMSO) δ 8.31 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.09 – 7.05 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.76 – 6.70 (m, 2H), 6.57 – 6.52 (m, 2H), 6.47 – 6.43 (m, 1H), 6.36 (d, J = 8.4 Hz, 1H), 6.32 – 6.27 (m, 1H), 6.10 (d, J = 1.8 Hz, 1H), 5.14 – 5.06 (m, 1H), 4.64 (d, J = 5.2 Hz, 1H), 4.37 – 4.30 (m, 1H), 4.29 – 4.21 (m, 1H), 4.15 – 4.06 (m, 1H), 4.00 – 3.93 (m, 1H), 3.83 – 3.79 (m, 1H), 3.22 – 3.14 (m, 2H), 3.02 – 2.97 (m, 6H), 2.94 – 2.88 (m, 9H), 2.77 – 2.70 (m, 2H), 2.45 – 2.37 (m, 3H), 2.18 – 2.08 (m, 2H), 1.97 – 1.91 (m, 3H), 1.79 – 1.70 (m, 1H), 1.66 – 1.57 (m, 3H), 1.54 – 1.48 (m, 2H), 1.46 – 1.38 (m, 2H).	836.4	836.4	
A133	^{1}H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1 H), 9.10 (s, 1 H), 7.01 - 7.30 (m, 5 H), 6.77 (br d, J = 6.63 Hz, 2 H), 6.57 - 6.65 (m, 2 H), 6.50 (br d, J = 7.63 Hz, 1 H), 6.31 - 6.45 (m, 2 H), 6.16 (s, 1 H), 5.08 (br dd, J = 13.45, 4.82 Hz, 1 H), 4.69 (br d, J = 4.75 Hz, 1 H), 4.41 (br d, J = 9.01 Hz, 1 H), 4.31 (br d, J = 16.76 Hz, 1 H), 4.15 (br d, J = 16.88 Hz, 1 H), 3.81	838.0	838.0	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	- 4.07 (m, 3 H), 3.46 - 3.53 (m, 1 H), 3.09 - 3.29 (m, 6 H), 2.87 - 3.08 (m, 8 H), 2.78 (br d, J = 9.13 Hz, 1 H), 2.58 - 2.67 (m, 2 H), 2.34 - 2.49 (m, 3 H), 2.14 - 2.28 (m, 2 H), 1.99 (br dd, J = 11.44, 7.44 Hz, 2 H), 1.56 - 1.84 (m, 6 H), 1.40 (br dd, J = 12.26, 8.38 Hz, 1 H).			
A134		838.0	838.0	
A135	^{1}H NMR (400MHz, DMSO-d6) 10.94 (s, 1H), 9.06 (s, 1H), 7.11 - 7.02 (m, 4H), 6.94 (s, 1H), 6.73 (br d, J=6.3 Hz, 2H), 6.60 - 6.53 (m, 2H), 6.46 (br d, J=8.3 Hz, 1H), 6.40 - 6.28 (m, 2H), 6.12 (s, 1H), 5.03 (br dd, J=4.8, 13.2 Hz, 1H), 4.65 (br d, J=4.9 Hz, 1H), 4.33 - 4.21 (m, 2H), 4.19 - 4.10 (m, 1H), 3.95 - 3.78 (m, 3H), 3.45 (br t, J=7.9 Hz, 1H), 3.24 - 3.16 (m, 2H), 3.12 - 3.00 (m, 5H), 2.99 - 2.88 (m, 7H), 2.82 - 2.74 (m, 1H), 2.58 (br d, J=14.8 Hz, 2H), 2.42 - 2.28 (m, 3H), 2.18 (br dd, J=6.5, 11.3 Hz, 1H), 2.12 - 2.03 (m, 1H), 2.01 - 1.90 (m, 2H), 1.75 (br t, J=10.9 Hz, 1H), 1.63 (br dd, J=5.0, 13.4 Hz, 5H), 1.35 (br dd, J=8.0, 12.5 Hz, 1H).	838.4	838.4	
A136	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1 H), 9.06 (s, 1 H), 6.88 - 7.14 (m, 5 H), 6.72 (br d, *J* = 6.25 Hz, 2 H), 6.51 - 6.62 (m, 2 H), 6.45 (dd, *J* = 8.25, 1.88 Hz, 1 H), 6.24 - 6.39 (m, 2 H), 6.11 (s, 1 H), 5.02 (br dd, *J* = 13.13, 5.00 Hz, 1 H), 4.64 (br d, *J* = 4.88 Hz, 1 H), 4.07 - 4.33 (m, 3 H), 3.73 - 3.96 (m, 3 H), 3.43 - 3.47 (m, 1 H), 3.04 - 3.25 (m, 7 H), 2.87 - 3.01 (m, 7 H), 2.76 (br t, *J* = 10.69 Hz, 1 H), 2.53 - 2.63 (m, 2 H), 2.26 - 2.42 (m, 3 H), 2.10 - 2.25 (m, 2 H), 1.86 - 2.00 (m, 2 H), 1.53 - 1.72 (m, 6 H), 1.34 (br dd, *J* = 12.63, 8.38 Hz, 1 H).	838.0	838.0	
A137	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.43 (s, 1H), 7.22 – 7.09 (m, 4H), 7.07 – 6.98 (m, 2H), 6.88 (d, J = 6.6 Hz, 2H), 6.67 (d, J = 8.6 Hz, 1H), 6.60 (s, 1H), 6.54 – 6.44 (m, 3H), 5.07 – 4.98 (m, 1H), 4.39 – 4.20 (m, 2H), 4.16 – 4.04 (m, 2H), 4.00 – 3.77 (m, 3H), 3.50 – 3.41 (m, 4H), 3.21 – 3.05 (m, 2H), 3.03 – 2.83 (m, 5H), 2.79 – 2.54 (m,	809.4	809.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	2H), 2.41 – 2.31 (m, 4H), 2.16 – 1.86 (m, 5H), 1.82 – 1.60 (m, 3H), 1.56 – 1.42 (m, 4H), 1.35 – 1.20 (m, 2H).			
A138	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.31 (s, 1H), 7.22 – 7.10 (m, 4H), 7.05 – 6.97 (m, 2H), 6.88 (d, J = 7.2 Hz, 2H), 6.69 – 6.56 (m, 2H), 6.54 – 6.44 (m, 3H), 5.07 – 4.98 (m, 1H), 4.35 (d, J = 9.8 Hz, 1H), 4.30 – 4.20 (m, 1H), 4.13 – 4.05 (m, 2H), 4.00 – 3.77 (m, 3H), 3.53 – 3.39 (m, 4H), 3.22 – 3.06 (m, 2H), 3.04 – 2.84 (m, 5H), 2.77 – 2.66 (m, 1H), 2.63 – 2.52 (m, 2H), 2.45 – 2.25 (m, 4H), 2.15 – 1.90 (m, 4H), 1.81 – 1.62 (m, 2H), 1.59 – 1.39 (m, 4H), 1.38 – 1.24 (m, 1H).	809.4	809.4	
A139	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.31 (s, 1H), 7.25 – 7.16 (m, 6H), 6.97 (dd, J = 19.6, 7.6 Hz, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 6.52 (dd, J = 8.4, 2.4 Hz, 1H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.30 (dd, J = 33.6, 12.8 Hz, 2H), 4.13 – 4.07 (m, 2H), 3.98 – 3.82 (m, 2H), 3.50 (d, J = 36.4 Hz, 6H), 2.94 – 2.84 (m, 4H), 2.68 (dd, J = 34.4, 23.4 Hz, 2H), 2.42 (dd, J = 26.7, 9.0 Hz, 4H), 2.13 – 1.69 (m, 8H), 1.43 (dd, J = 30.5, 20.8 Hz, 6H).	794.4	794.5	
A140	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.38 (s, 1H), 7.25 – 7.15 (m, 6H), 6.98 (dd, J = 19.6, 7.6 Hz, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.60 (s, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.03 (dd, J = 13.2, 4.8 Hz, 1H), 4.30 (dd, J = 34.4, 13.2 Hz, 2H), 4.09 (d, J = 16.8 Hz, 2H), 3.95 (t, J = 9.6 Hz, 1H), 3.80 (d, J = 12.4 Hz, 1H), 3.55 – 3.43 (m, 6H), 3.24 – 3.08 (m, 2H), 2.96 – 2.85 (m, 4H), 2.75 – 2.56 (m, 2H), 2.42 – 2.37 (m, 2H), 2.16 – 1.86 (m, 6H), 1.75 (dd, J = 26.2, 15.1 Hz, 2H), 1.43 (dd, J = 31.0, 21.4 Hz, 6H).	794.4	794.6	
A141	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.38 (s, 1H), 7.25 – 7.15 (m, 6H), 6.98 (dd, J = 19.6, 7.6 Hz, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.60 (s, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.30 (dd, J = 34.0, 13.2 Hz, 2H), 4.09 (d, J = 16.8 Hz, 2H), 3.95	793.4	793.6	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	(t, J = 9.6 Hz, 1H), 3.83 – 3.77 (m, 1H), 3.56 – 3.47 (m, 4H), 3.37 – 3.31 (m, 2H), 3.15 (s, 2H), 2.94 – 2.83 (m, 4H), 2.75 – 2.56 (m, 2H), 2.45 – 2.36 (m, 3H), 2.18 – 1.85 (m, 6H), 1.82 – 1.69 (m, 2H), 1.51 – 1.34 (m, 6H)..			
A142	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.18 (s, 1H), 7.26 – 7.16 (m, 5H), 7.03 (s, 1H), 6.98 – 6.91 (m, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 8.4, 2.4 Hz, 1H), 5.02 (dd, J = 13.2, 4.8 Hz, 1H), 4.29 – 4.09 (m, 4H), 3.92 – 3.86 (m, 1H), 3.78 (d, J = 11.2 Hz, 1H), 3.58 – 3.43 (m, 6H), 3.24 – 3.05 (m, 2H), 2.99 – 2.84 (m, 5H), 2.78 – 2.69 (m, 1H), 2.44 – 2.29 (m, 3H), 2.13 – 1.91 (m, 5H), 1.82 – 1.66 (m, 2H), 1.51 – 1.34 (m, 6H).	793.4	793.6	
A143	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.18 (s, 1H), 7.26 – 7.16 (m, 5H), 7.03 (s, 1H), 6.98 – 6.91 (m, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 8.4, 2.4 Hz, 1H), 5.02 (dd, J = 13.2, 4.8 Hz, 1H), 4.29 – 4.09 (m, 4H), 3.92 – 3.86 (m, 1H), 3.78 (d, J = 11.2 Hz, 1H), 3.58 – 3.43 (m, 6H), 3.24 – 3.05 (m, 2H), 2.99 – 2.84 (m, 5H), 2.78 – 2.69 (m, 1H), 2.44 – 2.29 (m, 3H), 2.13 – 1.91 (m, 5H), 1.82 – 1.66 (m, 2H), 1.51 – 1.34 (m, 6H).	794.4	794.7	
A1448	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.26 – 7.16 (m, 5H), 7.03 (s, 1H), 6.98 – 6.92 (m, 3H), 6.70 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.02 (dd, J = 13.2, 4.8 Hz, 1H), 4.38 – 4.04 (m, 5H), 3.94 – 3.74 (m, 3H), 3.14 (s, 2H), 3.04 – 2.82 (m, 6H), 2.78 – 2.54 (m, 3H), 2.47 – 2.29 (m, 4H), 2.14 – 1.68 (m, 8H), 1.53 – 1.35 (m, 6H).	794.4	794.5	
A145	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.26 (s, 1H), 7.20 – 6.98 (m, 5H), 6.86 – 6.78 (m, 2H), 6.61 (d, J = 8.8 Hz, 2H), 6.55 – 6.42 (m, 3H), 6.25 (d, J = 13.6 Hz, 1H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.47 – 4.22 (m, 3H), 4.10 (d, J = 16.8 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.80 (d, J = 11.2 Hz, 1H), 3.22 – 3.10 (m,	810.4	810.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	2H), 3.03 – 2.84 (m, 9H), 2.76 – 2.58 (m, 2H), 2.49 – 2.33 (m, 4H), 2.22 – 2.06 (m, 2H), 1.99 – 1.86 (m, 3H), 1.76 – 1.57 (m, 4H), 1.52 – 1.37 (m, 4H).			
A146	1H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 8.31 (s, 1H), 7.32 (dd, J = 47.6, 7.6 Hz, 2H), 7.13 – 7.07 (m, 3H), 6.85 – 6.79 (m, 2H), 6.63 – 6.45 (m, 5H), 6.25 (d, J = 12.8 Hz, 1H), 5.08 (dd, J = 13.2, 4.8 Hz, 1H), 4.57 – 4.33 (m, 4H), 4.21 (d, J = 17.2 Hz, 1H), 3.05 – 2.85 (m, 8H), 2.65 – 2.53 (m, 2H), 2.47 – 2.33 (m, 4H), 2.10 – 1.81 (m, 8H), 1.74 – 1.36 (m, 10H).	809.4	809.8	
A147	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.14 (s, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.11 – 7.07 (m, 3H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.84 – 6.78 (m, 2H), 6.64 – 6.56 (m, 2H), 6.55 – 6.41 (m, 3H), 6.25 (d, *J* = 13.6 Hz, 1H), 5.07 – 4.99 (m, 1H), 4.47 – 4.40 (m, 1H), 4.38 – 4.30 (m, 1H), 4.30 – 4.20 (m, 1H), 4.13 – 4.04 (m, 1H), 4.00 – 3.89 (m, 1H), 3.84 – 3.76 (m, 1H), 3.19 – 3.09 (m, 2H), 3.06 – 2.82 (m, 10H), 2.75 – 2.67 (m, 1H), 2.63 – 2.54 (m, 1H), 2.43 – 2.36 (m, 3H), 2.22 – 2.05 (m, 2H), 1.98 – 1.88 (m, 3H), 1.79 – 1.58 (m, 4H), 1.52 – 1.38 (m, 4H).	810.4	810.4	
A148	1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.13 (s, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.13 – 7.06 (m, 3H), 6.84 – 6.79 (m, 2H), 6.64 – 6.57 (m, 2H), 6.55 – 6.42 (m, 3H), 6.26 (d, J = 13.6 Hz, 1H), 5.12 – 5.04 (m, 1H), 4.56 – 4.48 (m, 2H), 4.47 – 4.42 (m, 1H), 4.41 – 4.33 (m, 1H), 4.24 – 4.16 (m, 1H), 3.04 – 2.80 (m, 10H), 2.68 – 2.55 (m, 2H), 2.47 – 2.36 (m, 3H), 2.23 – 2.13 (m, 1H), 2.09 – 1.83 (m, 7H), 1.74 – 1.56 (m, 5H), 1.54 – 1.36 (m, 4H).	809.4	809.4	
A149	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.24 – 9.09 (m, 1H), 7.15 – 7.00 (m, 4H), 6.93 (s, 1H), 6.85 – 6.76 (m, 2H), 6.64 – 6.57 (m, 2H), 6.56 – 6.41 (m, 3H), 6.31 – 6.21 (m, 1H), 5.07 – 4.98 (m, 1H), 4.44 (d, J = 5.2 Hz, 1H), 4.32 – 4.09 (m, 3H), 3.92 – 3.75 (m, 2H), 3.18 – 3.08 (m, 2H), 3.07 – 2.81 (m,	810.4	810.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	10H), 2.79 – 2.63 (m, 1H), 2.63 – 2.56 (m, 1H), 2.43 – 2.27 (m, 3H), 2.25 – 2.03 (m, 2H), 2.02 – 1.86 (m, 3H), 1.76 – 1.55 (m, 4H), 1.52 – 1.34 (m, 4H).			
A150	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.15 (s, 1H), 7.12 – 6.78 (m, 7H), 6.64 – 6.44 (m, 5H), 6.25 (d, *J* = 14.0 Hz, 1H), 5.02 (d, *J* = 12.8 Hz, 1H), 4.44 (s, 1H), 4.32 – 4.09 (m, 3H), 3.93 – 3.75 (m, 2H), 3.03 – 2.86 (m, 10H), 2.79 – 2.70 (m, 2H), 2.43 – 2.30 (m, 4H), 2.22 – 2.05 (m, 3H), 1.92 (s, 3H), 1.73 – 1.58 (m, 4H), 1.51 – 1.38 (m, 4H).	740.6	740.6	
A151	^{1}H NMR (400 MHz, MeOD) δ 7.16 (s, 1H), 7.12 (s, 1H), 7.09 – 7.03 (m, 3H), 6.84 – 6.77 (m, 2H), 6.63 (dd, *J* = 8.8, 5.4 Hz, 2H), 6.50 (ddd, *J* = 8.2, 5.4, 2.7 Hz, 2H), 6.07 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.75 (dd, *J* = 12.0, 2.2 Hz, 1H), 5.08 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.52 (d, *J* = 5.2 Hz, 1H), 4.36 (d, *J* = 2.4 Hz, 3H), 4.15 (s, 1H), 4.10 – 4.01 (m, 1H), 3.55 (d, *J* = 27.4 Hz, 3H), 3.49 (d, *J* = 7.2 Hz, 2H), 3.42 (t, *J* = 4.7 Hz, 2H), 3.21 (d, *J* = 7.3 Hz, 1H), 3.03 – 2.94 (m, 3H), 2.93 – 2.83 (m, 2H), 2.81 – 2.76 (m, 1H), 2.51 – 2.38 (m, 1H), 2.35 – 2.24 (m, 1H), 2.23 – 2.08 (m, 2H), 1.99 (d, *J* = 13.1 Hz, 3H), 1.78 (dd, *J* = 29.6, 13.5 Hz, 4H), 1.59 (t, *J* = 11.9 Hz, 3H), 1.15 (dd, *J* = 24.1, 10.5 Hz, 2H)	810.4	810.3	
A152	^{1}H NMR (400 MHz, MeOD) δ 7.10 (s, 1H), 7.08 – 7.04 (m, 3H), 7.02 (s, 1H), 6.80 (dd, *J* = 6.3, 3.1 Hz, 2H), 6.63 (dd, *J* = 10.7, 5.4 Hz, 2H), 6.50 (t, *J* = 8.6 Hz, 2H), 6.06 (dd, *J* = 8.4, 2.2 Hz, 1H), 5.74 (dd, *J* = 12.0, 2.1 Hz, 1H), 5.07 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.52 (d, *J* = 5.3 Hz, 1H), 4.33 (d, *J* = 2.0 Hz, 2H), 4.29 (dd, *J* = 10.8, 2.7 Hz, 1H), 3.97 (dd, *J* = 10.8, 8.4 Hz, 1H), 3.90 (d, *J* = 12.3 Hz, 1H), 3.52 – 3.45 (m, 2H), 3.41 (q, *J* = 7.1 Hz, 2H), 3.13 (dd, *J* = 27.4, 10.6 Hz, 2H), 3.02 – 2.91 (m, 3H), 2.86 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.81 – 2.71 (m, 1H), 2.52 – 2.36 (m, 4H), 2.34 – 2.23 (m, 1H), 2.22 – 2.09 (m, 2H), 2.06 – 2.00 (m, 1H), 1.94 (d, *J* = 12.5 Hz, 2H), 1.84 – 1.71 (m, 3H), 1.68 – 1.57 (m, 2H), 1.53 (t, *J*	810.4	810.3	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	= 12.0 Hz, 2H), 1.05 (dd, *J* = 21.7, 12.0 Hz, 2H).			
A153	1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.26 (s, 1H), 7.44 – 7.36 (m, 1H), 7.26 – 7.15 (m, 6H), 6.95 (d, J = 7.2 Hz, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 6.54 – 6.48 (m, 1H), 5.13 – 5.04 (m, 1H), 4.50 (t, J = 10.2 Hz, 2H), 4.40 – 4.34 (m, 1H), 4.24 – 4.17 (m, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.57 (s, 2H), 3.52 (s, 2H), 3.36 – 3.29 (m, 2H), 3.00 – 2.86 (m, 3H), 2.82 – 2.75 (m, 2H), 2.66 – 2.54 (m, 1H), 2.47 – 2.34 (m, 1H), 2.10 (d, J = 6.8 Hz, 2H), 2.00 – 1.86 (m, 6H), 1.84 – 1.75 (m, 3H), 1.72 – 1.61 (m, 4H), 1.51 – 1.36 (m, 3H), 0.95 – 0.82 (m, 2H).	793.4	793.4	
A154	1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.30 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.28 – 7.15 (m, 6H), 6.95 (d, J = 7.2 Hz, 2H), 6.69 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 6.53 – 6.48 (m, 1H), 5.12 – 5.05 (m, 1H), 4.54 – 4.48 (m, 2H), 4.41 – 4.34 (m, 1H), 4.24 – 4.17 (m, 1H), 4.12 (d, J = 4.8 Hz, 1H), 3.57 (s, 2H), 3.52 (s, 2H), 3.37 – 3.31 (m, 2H), 3.01 – 2.87 (m, 3H), 2.82 – 2.76 (m, 2H), 2.63 – 2.53 (m, 1H), 2.44 – 2.33 (m, 1H), 2.10 (d, J = 6.8 Hz, 2H), 2.01 – 1.86 (m, 6H), 1.81 (d, J = 12.0 Hz, 3H), 1.72 – 1.62 (m, 4H), 1.52 – 1.35 (m, 3H), 0.98 – 0.83 (m, 2H).	793.4	793.4	
A155	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.28 – 7.15 (m, 6H), 7.02 – 6.91 (m, 3H), 6.68 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 6.53 – 6.46 (m, 1H), 5.08 – 4.96 (m, 1H), 4.39 – 4.33 (m, 1H), 4.29 – 4.21 (m, 1H), 4.15 – 4.06 (m, 2H), 3.99 – 3.91 (m, 1H), 3.81 (d, J = 10.8 Hz, 1H), 3.56 – 3.51 (m, 3H), 3.36 – 3.30 (m, 1H), 3.19 – 3.14 (m, 1H), 3.00 – 2.84 (m, 5H), 2.76 – 2.59 (m, 2H), 2.59 – 2.53 (m, 1H), 2.43 – 2.34 (m, 1H), 2.17 – 2.02 (m, 3H), 1.99 – 1.91 (m, 2H), 1.83 – 1.76 (m, 3H), 1.73 – 1.62 (m, 3H), 1.53 – 1.36 (m, 3H), 1.01 (t, J = 7.2 Hz, 1H), 0.97 – 0.82 (m, 2H).	794.4	794.4	
A156	1H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 7.31 – 7.22 (m, 6H), 7.07 – 6.94 (m, 3H),	794.4	794.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	6.74 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 2.0 Hz, 1H), 6.59 – 6.53 (m, 1H), 5.13 – 5.03 (m, 1H), 4.45 – 4.37 (m, 1H), 4.34 – 4.27 (m, 1H), 4.22 – 4.11 (m, 2H), 4.05 – 3.98 (m, 1H), 3.89 – 3.84 (m, 1H), 3.63 – 3.60 (m, 2H), 3.58 (s, 3H), 3.24 – 3.19 (m, 1H), 3.13 – 2.86 (m, 6H), 2.79 (t, J = 10.4 Hz, 1H), 2.68 – 2.58 (m, 1H), 2.51 – 2.38 (m, 1H), 2.24 – 2.08 (m, 3H), 2.05 – 1.95 (m, 2H), 1.89 – 1.81 (m, 3H), 1.79 – 1.69 (m, 3H), 1.58 – 1.42 (m, 3H), 1.03 – 0.87 (m, 2H).			
A157	^{1}H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.26 – 7.15 (m, 5H), 7.03 (s, 1H), 6.94 (d, J = 6.6 Hz, 3H), 6.68 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 6.55 – 6.47 (m, 1H), 5.06 – 4.97 (m, 1H), 4.32 – 4.20 (m, 2H), 4.17 – 4.07 (m, 2H), 3.97 – 3.82 (m, 2H), 3.81 – 3.72 (m, 2H), 3.37 – 3.30 (m, 2H), 3.19 – 3.01 (m, 2H), 3.02 – 2.80 (m, 6H), 2.75 (t, J = 10.4 Hz, 1H), 2.61 – 2.54 (m, 1H), 2.41 – 2.28 (m, 1H), 2.16 – 2.03 (m, 3H), 2.00 – 1.90 (m, 2H), 1.84 – 1.74 (m, 3H), 1.72 – 1.61 (m, 3H), 1.53 – 1.36 (m, 3H), 0.98 – 0.84 (m, 2H).	794.4	794.4	
A158	^{1}H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.31 (s, 1H), 7.25 – 7.12 (m, 5H), 7.03 (s, 1H), 6.97 – 6.88 (m, 3H), 6.68 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 6.53 – 6.44 (m, 1H), 5.06 – 4.98 (m, 1H), 4.33 – 4.19 (m, 2H), 4.18 – 4.08 (m, 2H), 3.92 – 3.75 (m, 3H), 3.58 – 3.55 (m, 2H), 3.36 – 3.32 (m, 1H), 3.17 – 3.12 (m, 1H), 3.00 – 2.85 (m, 5H), 2.79 – 2.70 (m, 1H), 2.66 – 2.51 (m, 2H), 2.40 – 2.30 (m, 1H), 2.19 – 2.02 (m, 3H), 1.99 – 1.89 (m, 2H), 1.84 – 1.75 (m, 3H), 1.74 – 1.63 (m, 3H), 1.53 – 1.36 (m, 3H), 1.06 – 0.97 (m, 1H), 0.95 – 0.83 (m, 2H).	794.4	794.4	
A159	^{1}H NMR (400M Hz, MeOD) δ 10.92 (s, 1H), 9.11 (s, 1H), 7.17 (d, J =8.4 Hz, 1H), 7.11-7.08 (m, 3H), 7.01 (d, J =8.1 Hz, 1H), 6.82-6.80 (m, 2H), 6.60-6.58 (m, 2H), 6.48-6.40 (m, 2H), 6.01 (d, J =10.0 Hz, 1H), 5.74 (d, J =12.0 Hz, 1H), 5.05-5.00 (m, 1H), 4.43 (d, J =4.8 Hz, 2H), 4.37-4.34 (m, 1H), 4.25	810.4	810.3	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	(d, J =17.2 Hz, 1H), 4.10 (d, J =17.2 Hz, 1H), 3.98-3.92 (m, 1H), 3.83-3.79 (m, 1H), 3.41 (s, 2H), 3.35 (s, 2H), 3.25-3.18 (m, 1H), 2.99-2.85 (m, 5H), 2.73-2.67 (m, 1H), 2.40-2.33 (m, 1H), 2.19-2.08 (m, 4H), 2.07-2.00 (m, 2H), 1.84-1.81 (m, 2H), 1.72-1.66 (m, 4H), 1.49-1.39 (m, 3H), 1.23 (s, 1H)			
A160	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.14 (s, 1H), 7.39 - 7.37 (m, 1H), 7.30 - 7.28(m, 1H), 7.14 - 7.10 (m, 3H), 6.84 – 6.81 (m, 2H), 6.61 – 6.59 (m, 2H), 6.50 - 6.42 (m, 2H), 6.04 - 6.01 (m, 1H), 5.77 - 5.73 (m, 1H), 5.11 - 5.06 (m, 1H) , 4.55 (s, 2H) , 4.44 - 4.36 (m, 2H), 4.20 (d, J = 13.2 Hz, 1H), 3.00 - 2.86 (m, 5H), 2.62 - 2.57 (m, 1H), 2.44 – 2.40 (m, 2H), 2.20 - 2.16 (m, 2H), 2.08 - 1.96 (m, 4H), 1.87 - 1.83 (m, 2H), 1.72 – 1.69 (m, 5H), 1.48 – 1.42 (m, 3H), 1.24 (s, 6H), 0.96 - 0.93 (m, 2H)	809.4	809.5	
A161	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.16 (s, 1H), 7.40 - 7.37 (m, 1H), 7.28 - 7.26(m, 1H), 7.11 - 7.10 (m, 3H), 6.83 – 6.81 (m, 2H), 6.62 – 6.59 (m, 2H), 6.50 - 6.42 (m, 2H), 6.04 - 6.01 (m, 1H), 5.76 - 5.73 (m, 1H), 5.11 - 5.06 (m, 1H) , 4.52 (s, 2H) , 4.44 - 4.36 (m, 2H), 4.24 – 4.19 (m, 1H), 2.95 – 2.80 (m, 5H), 2.67 - 2.61 (m, 1H), 2.44 – 2.33 (m, 2H), 2.12 - 2.11 (m, 2H), 2.02 - 1.96 (m, 4H), 1.85 - 1.82 (m, 2H), 1.70 – 1.67 (m, 5H), 1.46 – 1.40 (m, 3H), 1.24 (s, 6H), 0.92 - 0.86 (m, 2H)	809.4	809.5	
A162	^{1}H NMR (400 MHz, MeOD) δ 7.37 (s, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.07 – 7.03 (m, 3H), 6.80 (s, 1H), 6.74 (dd, *J* = 6.3, 2.9 Hz, 3H), 6.64 (d, *J* = 2.2 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 2H), 6.49 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.12 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.62 (s, 2H), 4.43 (t, *J* = 13.7 Hz, 2H), 3.65 – 3.54 (m, 3H), 3.39 (s, 2H), 3.10 (s, 5H), 2.99 (dd, *J* = 9.7, 5.5 Hz, 2H), 2.88 (dd, *J* = 12.7, 4.7 Hz, 1H), 2.80 (dd, *J* = 6.5, 5.0 Hz, 1H), 2.47 (dd, *J* = 13.2, 4.6 Hz, 1H), 2.32 – 2.21 (m, 6H), 2.06 (dd, *J* = 21.6, 10.0 Hz, 5H), 1.89 (s, 2H), 1.83 – 1.75	821.4	821.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	(m, 2H), 1.70 (d, *J* = 9.8 Hz, 1H), 1.31 (d, *J* = 18.0 Hz, 5H)			
A163	^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.11 (s, 1H), 7.22 – 6.95 (m, 5H), 6.78 (d, J = 6.8 Hz, 2H), 6.65 – 6.39 (m, 3H), 6.10 (d, J = 13.6 Hz, 1H), 5.67 (d, J = 8.0 Hz, 1H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.40 – 4.31 (m, 1H), 4.18 (dd, J = 62.8, 16.8 Hz, 2H), 4.01 – 3.89 (m, 1H), 3.81 (d, J = 11.6 Hz, 1H), 3.57 – 3.45 (m, 4H), 3.23 – 3.14 (m, 2H), 3.02 – 2.82 (m, 8H), 2.74 (d, J = 10.4 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.43 – 2.31 (m, 1H), 2.20 – 2.01 (m, 4H), 1.99 – 1.84 (m, 3H), 1.76 – 1.58 (m, 4H), 1.55 – 1.37 (m, 3H), 1.00 – 0.82 (m, 2H).	840.4	840.4	
A164	^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.11 (s, 1H), 7.14 – 7.00 (m, 4H), 6.93 (s, 1H), 6.78 (d, J = 6.8 Hz, 2H), 6.60 – 6.43 (m, 3H), 6.10 (d, J = 13.6 Hz, 1H), 5.67 (d, J = 8.0 Hz, 1H), 5.02 (dd, J = 13.2, 4.8 Hz, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.32 – 4.11 (m, 3H), 3.93 – 3.76 (m, 2H), 3.57 – 3.45 (m, 4H), 3.24 – 3.14 (m, 2H), 2.98 – 2.84 (m, 8H), 2.80 – 2.72 (m, 1H), 2.64 – 2.57 (m, 1H), 2.39 – 2.30 (m, 1H), 2.17 – 2.07 (m, 3H), 1.98 – 1.84 (m, 3H), 1.75 – 1.59 (m, 4H), 1.54 – 1.38 (m, 3H), 1.24 (s, 1H), 0.98 – 0.85 (m, 2H).	840.4	840.4	
A165	^{1}H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 7.19 – 6.97 (m, 5H), 6.78 (d, *J* = 6.8 Hz, 2H), 6.64 – 6.46 (m, 3H), 6.10 (d, *J* = 13.6 Hz, 1H), 5.67 (d, *J* = 8.0 Hz, 1H), 5.07 – 4.93 (m, 1H), 4.62 (d, *J* = 5.2 Hz, 1H), 4.40 – 4.34 (m, 1H), 4.31 – 4.09 (m, 2H), 3.97 (d, *J* = 8.8 Hz, 1H), 3.86 – 3.79 (m, 1H), 3.62 – 3.46 (m, 5H), 3.29 – 3.07 (m, 5H), 2.91 (d, *J* = 10.6 Hz, 6H), 2.59 (s, 1H), 2.42 – 2.34 (m, 1H), 2.17 – 1.88 (m, 6H), 1.72 – 1.36 (m, 7H), 1.24 (s, 1H), 0.98 – 0.84 (m, 2H).	840.4	840.4	
A166	1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1 H), 8.26 (s, 1 H), 7.45 (s, 1 H), 7.12-7.02 (m, 3 H), 7.00 (s, 1 H), 6.78 (d, J=6.8 Hz, 2 H), 6.58-6.54 (m, 2 H), 6.49-6.46 (m, 1 H), 6.10 (d, J=13.6 Hz, 1 H), 5.67 (d, J=8.4 Hz, 1 H),	840.4	840.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	5.09-5.05 (m, 1 H), 4.63-4.62 (m, 1 H), 4.55 (s, 2 H), 4.34 (d, J=16.8 Hz, 1 H), 4.21 (d, J=17.2 Hz, 1 H), 3.57-3.46 (m, 4 H), 3.24-3.20 (m, 2 H), 2.93-2.78 (m, 8 H), 2.63-2.57 (m, 1 H), 2.43-2.31 (m, 1 H), 2.18-2.09 (m, 2 H), 2.00-1.86 (m, 7 H), 1.71-1.60 (m, 5 H), 1.52-1.40 (m, 3 H), 0.97-0.85 (m, 2 H).			
A167	1H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 7.45 (s, 1H), 7.14 – 7.03 (m, 3H), 7.00 (s, 1H), 6.78 (d, J = 6.8 Hz, 2H), 6.59 – 6.43 (m, 3H), 6.10 (d, J = 13.6 Hz, 1H), 5.68 (d, J = 8.0 Hz, 1H), 5.07 (dd, J = 13.2, 5.2 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.48 – 4.41 (m, 2H), 4.27 (dd, J = 52.4, 17.2 Hz, 2H), 3.56 – 3.46 (m, 5H), 3.26 – 3.19 (m, 2H), 2.95 – 2.77 (m, 8H), 2.62 – 2.56 (m, 1H), 2.40 – 2.31 (m, 1H), 2.14 – 2.08 (m, 2H), 1.98 – 1.84 (m, 7H), 1.74 – 1.61 (m, 5H), 1.51 – 1.38 (m, 3H), 0.96 – 0.85 (m, 2H).	839.4	839.5	
A168	1H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 9.56 – 8.58 (m, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.13 – 7.05 (m, 3H), 6.78 (d, J = 7.2 Hz, 2H), 6.59 – 6.53 (m, 2H), 6.50 – 6.45 (m, 1H), 6.10 (d, J = 13.2 Hz, 1H), 5.68 (d, J = 8.0 Hz, 1H), 5.08 (dd, J = 13.2, 4.8 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.51 (s, 2H), 4.38 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 3.22 (d, J = 14.4 Hz, 2H), 2.93 (s, 3H), 2.84 – 2.78 (m, 2H), 2.69 – 2.55 (m, 2H), 2.49 – 2.34 (m, 2H), 2.25 – 2.04 (m, 4H), 2.00 – 1.84 (m, 8H), 1.76 – 1.58 (m, 6H), 1.56 – 1.33 (m, 4H), 1.25 – 1.15 (m, 1H), 0.95 – 0.85 (m, 2H).	839.4	839.5	
A169	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.37 (s, 1H), 7.12 – 7.02 (m, 4H), 6.93 (s, 1H), 6.78 (d, J = 6.8 Hz, 2H), 6.60 – 6.53 (m, 2H), 6.48 (d, J = 8.4 Hz, 1H), 6.10 (d, J = 13.6 Hz, 1H), 5.67 (d, J = 8.0 Hz, 1H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.32 – 4.11 (m, 3H), 3.94 – 3.77 (m, 2H), 3.55 – 3.48 (m, 4H), 3.28 – 3.13 (m, 4H), 2.92 (s, 3H), 2.90 – 2.72 (m, 4H), 2.68 – 2.52 (m, 2H), 2.38 – 1.97 (m, 6H), 1.87 (d, J	840.4	840.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	= 11.6 Hz, 2H), 1.74 – 1.59 (m, 4H), 1.47 – 1.39 (m, 2H), 0.97 – 0.85 (m, 2H).			
A170	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.15 – 7.02 (m, 4H), 6.94 (s, 1H), 6.77 (d, J = 6.6 Hz, 2H), 6.61 – 6.53 (m, 3H), 6.49 – 6.37 (m, 2H), 5.10 – 4.96 (m, 1H), 4.60 (d, J = 5.2 Hz, 1H), 4.33 – 4.10 (m, 3H), 3.93 – 3.76 (m, 2H), 3.31 – 3.12 (m, 5H), 3.02 – 2.85 (m, 8H), 2.82 – 2.73 (m, 1H), 2.64 – 2.52 (m, 3H), 2.41 – 2.16 (m, 4H), 2.14 – 2.05 (m, 1H), 2.00 – 1.91 (m, 1H), 1.84 – 1.59 (m, 5H), 1.32 – 1.17 (m, 2H).	800.4	800.4	
A171	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.14 – 7.01 (m, 4H), 6.94 (s, 1H), 6.77 (d, J = 6.6 Hz, 2H), 6.61 – 6.53 (m, 3H), 6.49 – 6.38 (m, 2H), 5.08 – 4.96 (m, 1H), 4.60 (d, J = 5.4 Hz, 1H), 4.34 – 4.08 (m, 3H), 3.95 – 3.75 (m, 2H), 3.31 – 3.13 (m, 5H), 3.03 – 2.84 (m, 8H), 2.82 – 2.73 (m, 1H), 2.63 – 2.52 (m, 3H), 2.41 – 2.15 (m, 4H), 2.13 – 2.03 (m, 1H), 2.01 – 1.91 (m, 1H), 1.84 – 1.58 (m, 5H), 1.32 – 1.16 (m, 2H).	800.4	800.4	
A172	1H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 8.32 (s, 1H), 7.45 (s, 1H), 7.16 – 6.96 (m, 5H), 6.78 (d, J = 6.8 Hz, 2H), 6.58 – 6.46 (m, 3H), 6.10 (d, J = 13.6 Hz, 1H), 5.68 (d, J = 8.0 Hz, 1H), 5.07 (dd, J = 13.2, 4.8 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.45 (s, 2H), 4.34 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 16.8 Hz, 1H), 2.93 (s, 3H), 2.83 – 2.78 (m, 2H), 2.70 – 2.54 (m, 2H), 2.48 – 2.24 (m, 2H), 2.21 – 2.06 (m, 4H), 2.00 – 1.85 (m, 8H), 1.73 – 1.59 (m, 6H), 1.54 – 1.34 (m, 4H), 0.95 – 0.87 (m, 2H).	839.4	839.6	
A173	^{1}H NMR (400MHz, DMSO-d6) 10.93 (br s, 1H), 9.15 (br s, 1H), 7.13 - 7.02 (m, 4H), 6.94 (s, 1H), 6.78 - 6.72 (m, 2H), 6.61 - 6.53 (m, 2H), 6.48 (dd, J=2.3, 8.4 Hz, 1H), 6.24 - 6.14 (m, 2H), 5.03 (dd, J=5.2, 13.3 Hz, 1H), 4.67 (br d, J=5.1 Hz, 1H), 4.32 - 4.22 (m, 2H), 4.19 - 4.11 (m, 1H), 3.95 - 3.86 (m, 2H), 3.82 (br d, J=11.6 Hz, 1H), 3.19 (br d, J=9.1 Hz, 2H), 3.05 - 2.84 (m, 13H), 2.81 - 2.73 (m, 1H), 2.62 - 2.54 (m, 2H), 2.41 - 2.30 (m, 3H),	856.4	856.3	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	2.21 - 2.05 (m, 2H), 1.97 (br dd, J=7.9, 11.8 Hz, 2H), 1.77 - 1.57 (m, 6H), 1.37 (br dd, J=8.3, 12.3 Hz, 1H).			
A174	^{1}H NMR (400MHz, DMSO-d6) 10.94 (br s, 1H), 9.16 (br s, 1H), 7.18 (d, *J*=8.3 Hz, 1H), 7.14 - 6.98 (m, 4H), 6.75 (br d, *J*=6.3 Hz, 2H), 6.63 - 6.54 (m, 2H), 6.52 - 6.44 (m, 1H), 6.28 - 6.14 (m, 2H), 5.03 (dd, *J*=5.0, 13.3 Hz, 1H), 4.67 (br d, *J*=5.1 Hz, 1H), 4.36 (br d, *J*=9.3 Hz, 1H), 4.31 - 4.19 (m, 1H), 4.11 (br d, *J*=16.9 Hz, 1H), 4.01 - 3.78 (m, 3H), 3.19 (br d, *J*=8.5 Hz, 3H), 3.05 - 2.83 (m, 13H), 2.80 - 2.71 (m, 1H), 2.63 - 2.55 (m, 2H), 2.41 - 2.27 (m, 2H), 2.13 (br t, *J*=11.3 Hz, 2H), 1.96 (br dd, *J*=7.3, 12.0 Hz, 2H), 1.77 - 1.56 (m, 6H), 1.37 (br dd, *J*=8.3, 12.4 Hz, 1H).	856.4	856.3	
A175	^{1}H NMR (400MHz, DMSO-d6) 10.97 (br s, 1H), 9.74 - 8.67 (m, 1H), 7.46 (br s, 1H), 7.20 - 6.99 (m, 4H), 6.76 (br d, J=5.8 Hz, 2H), 6.65 - 6.40 (m, 3H), 6.20 (br d, J=10.3 Hz, 2H), 5.08 (br d, J=8.8 Hz, 1H), 4.68 (br s, 1H), 4.46 (br s, 2H), 4.37 - 4.30 (m, 1H), 4.28 - 4.14 (m, 1H), 3.88 (br s, 1H), 3.28 (br s, 1H), 3.05 - 2.78 (m, 12H), 2.59 (br d, J=16.0 Hz, 2H), 2.42 - 2.28 (m, 3H), 2.16 (br d, J=7.3 Hz, 1H), 2.08 - 1.82 (m, 7H), 1.66 (br s, 7H), 1.38 (br d, J=8.4 Hz, 1H).	855.4	855.3	
A176	^{1}H NMR (400MHz, DMSO-d6) 10.98 (br s, 1H), 9.54 - 8.54 (m, 1H), 7.48 - 7.20 (m, 2H), 7.09 (br s, 3H), 6.76 (br d, *J*=4.0 Hz, 2H), 6.65 - 6.41 (m, 3H), 6.20 (br d, *J*=9.8 Hz, 2H), 5.09 (br d, *J*=8.6 Hz, 1H), 4.68 (br s, 1H), 4.52 (br s, 2H), 4.38 (br d, *J*=17.0 Hz, 1H), 4.22 (br d, *J*=16.8 Hz, 1H), 3.89 (br s, 1H), 3.28 (br s, 1H), 3.02 - 2.78 (m, 13H), 2.59 (br d, *J*=16.5 Hz, 2H), 2.45 - 2.29 (m, 3H), 2.15 (br s, 1H), 1.97 (br d, *J*=11.9 Hz, 6H), 1.67 (br s, 7H), 1.37 (br s, 1H).	855.4	855.3	
A177	^{1}H NMR (400 MHz, MeOD) δ 7.43 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 6.8 Hz, 3H), 6.80 (d, *J* = 6.0 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.64 (s, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 6.25 (d, *J* = 8.3 Hz, 2H), 6.14 (d, *J* = 8.4 Hz, 2H), 5.14 (dd, *J* = 13.2, 5.0 Hz,	790.4	791.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	1H), 4.69 (s, 2H), 4.43 (q, *J* = 17.1 Hz, 2H), 4.15 (d, *J* = 4.8 Hz, 1H), 3.67 (d, *J* = 11.4 Hz, 2H), 3.49 (s, 2H), 3.43 (s, 2H), 3.17 – 2.95 (m, 6H), 2.89 (dd, *J* = 21.9, 9.2 Hz, 1H), 2.78 (d, *J* = 15.5 Hz, 1H), 2.50 (dt, *J* = 13.5, 8.6 Hz, 1H), 2.28 (d, *J* = 13.0 Hz, 2H), 2.03 (t, *J* = 22.0 Hz, 6H), 1.80 (d, *J* = 15.6 Hz, 3H), 1.59 (t, *J* = 11.1 Hz, 4H), 1.18 (d, *J* = 12.0 Hz, 2H).			
A178	^{1}H NMR (400 MHz, MeOD) δ 7.37 (s, 1H), 7.13 (dd, *J* = 16.9, 7.4 Hz, 4H), 6.81 (d, *J* = 7.4 Hz, 2H), 6.71 – 6.60 (m, 2H), 6.51 (d, *J* = 8.3 Hz, 1H), 6.26 (d, *J* = 8.4 Hz, 2H), 6.16 (d, *J* = 8.4 Hz, 2H), 5.12 (dd, *J* = 13.5, 5.3 Hz, 1H), 4.62 (s, 2H), 4.42 (d, *J* = 7.7 Hz, 1H), 4.16 (d, *J* = 4.7 Hz, 1H), 3.66 (d, *J* = 12.4 Hz, 2H), 3.51 (s, 2H), 3.44 (s, 2H), 3.17 – 2.99 (m, 6H), 2.88 (d, *J* = 12.8 Hz, 1H), 2.77 (d, *J* = 14.4 Hz, 1H), 2.39 – 2.23 (m, 4H), 2.01 (d, *J* = 13.1 Hz, 6H), 1.80 (d, *J* = 14.7 Hz, 3H), 1.60 (t, *J* = 11.2 Hz, 4H), 1.18 (d, *J* = 11.2 Hz, 2H).	790.4	791.5	
A179	1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.82 (d, J = 8.4 Hz, 1H), 8.27 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.15 – 7.01 (m, 3H), 6.78 (d, J = 6.8 Hz, 2H), 6.61 – 6.52 (m, 2H), 6.48 (d, J = 8.0 Hz, 1H), 6.14 – 6.02 (m, 1H), 5.68 (d, J = 8.0 Hz, 1H), 4.80 – 4.70 (m, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.48 (s, 2H), 3.55 – 3.49 (m, 3H), 3.27 – 3.17 (m, 1H), 3.01 – 2.82 (m, 6H), 2.79 – 2.71 (m, 3H), 2.23 – 2.08 (m, 4H), 2.03 – 1.79 (m, 8H), 1.75 – 1.61 (m, 5H), 1.51 – 1.37 (m, 3H), 1.00 – 0.85 (m, 2H).	827.4	828.3	
A180	1 H NMR (400 MHz, DMSO-d6) δ 10.92 (s, 1 H), 7.18 (d, J = 8.4 Hz, 1 H), 7.14-6.98 (m, 4 H), 6.75 (d, J = 6.0 Hz, 2 H), 6.60-6.54 (m, 2 H), 6.51-6.45 (m, 1 H), 6.26-6.14 (m, 2 H), 5.03 (dd, J = 13.2, 4.8 Hz, 1 H), 4.67 (d, J = 5.6 Hz, 1 H), 4.36 (d, J = 8.0 Hz, 1 H), 4.30-4.07 (m, 2 H), 4.00-3.93 (m, 1 H), 3.82 (d, J = 11.6 Hz, 1 H), 3.27-3.12 (m, 6 H), 3.01-2.84 (m, 8 H), 2.78-2.67 (m, 1 H), 2.62-2.54 (m, 2 H), 2.42-2.29 (m, 3 H), 2.19-2.04 (m, 2 H),	813.9	814.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	1.98-1.89 (m, 1 H), 1.78-1.59 (m, 4 H), 1.48-1.22 (m, 5 H).			
A181	1H NMR (400 MHz, MeOD-d_4) δ8.52 (s, 1H), 7.40–7.33 (m, 2H), 7.10 – 7.08 (m, 3H), 6.80 - 6.78 (m, 2H), 6.67(d, J = 8.4, 1H), 6.63 – 6.59 (m, 3H), 6.52 – 6.49 (m, 1H), 6.28 (d, J = 8.4, 2H), 5.14-5.10 (m, 1H), 5.14 – 5.10 (m, 1H), 4.58 (s, 2H), 4.46 – 4.35 (m, 2H), 4.16 (d, J = 4.0, 1H), 3.12 – 3.09 (m, 2H), 3.10 – 2.97 (m, 4H), 2.89 – 2.86 (m, 3H), 2.78 – 2.74 (m, 3H), 2.64 – 2.42 (m, 4H) , 2.18 – 2.12 (m, 2H), 2.08 – 2.05 (m, 4H), 1.87 – 1.83 (m, 2H) , 1.76 – 1.73 (m, 3H), 1.64 – 1.60 (m, 2H) , 1.58 – 1.53 (m, 2H), 1.34 – 1.28 (m, 1H).	790.4	791.4	
A182	1H NMR (400 MHz, MeOD-d_4) δ7.36 (s, 1H), 7.15 – 7.08 (m, 4H), 6.80 - 6.78 (m, 2H), 6.69 - 6.63 (m, 4H), 6.52 – 6.49 (m, 1H), 6.31 (d, J = 8.8, 2H), 5.14-5.09 (m, 1H), 4.94 – 4.91 (m, 1H) , 4.63 – 4.60 (m, 2H), 4.49 – 4.36 (m, 2H), 4.18 (d, J = 4.8, 1H), 3.57 – 3.47 (m, 3H), 3.12 – 2.97 (m, 6H), 2.95 – 2.85 (m, 3H), 2.79 – 2.71 (m, 2H), 2.49– 2.42 (m, 1H) , 2.26 – 2.14 (m, 7H), 2.09 – 2.05 (m, 2H), 1.82 – 1.80 (m, 2H) , 1.78– 1.74 (m, 1H), 1.69 – 1.64 (m, 4H).	790.4	791.4	
A183	1 H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1 H), 7.44-7.32 (m, 1 H), 7.30-7.19 (m, 1 H), 7.19-7.08 (m, 3 H), 6.82 (d, J = 6.8 Hz, 2 H), 6.66-6.56 (m, 2 H), 6.54-6.39 (m, 1 H), 6.18 (d, J = 8.4 Hz, 2 H), 6.06 (d, J = 8.4 Hz, 2 H), 5.13-5.03 (m, 1 H), 4.56-4.45 (m, 2 H), 4.41-4.29 (m, 2 H), 4.25-4.08 (m, 2 H), 3.96-3.88 (m, 2 H), 3.32-3.19 (m, 5 H), 3.03-2.78 (m, 6 H), 2.64-2.55 (m, 1 H), 2.45-2.31 (m, 3 H), 2.15-2.05 (m, 1 H), 2.00-1.84 (m, 5 H), 1.73-1.62 (m, 5 H).	766.4	767.5	
A184	1H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.12 – 7.05 (m, 3H), 6.77 (d, J = 6.4 Hz, 2H), 6.60 – 6.51 (m, 2H), 6.50 – 6.44 (m, 1H), 6.10 (d, J = 13.2 Hz, 1H), 5.66 (d, J = 8.0 Hz, 1H), 5.12 – 5.04 (m, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.54 – 4.48 (m, 2H), 4.39 – 4.32	810.4	811.4	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	(m, 1H), 4.27 – 4.17 (m, 1H), 3.88 – 3.80 (m, 2H), 3.73 – 3.68 (m, 2H), 3.24 – 3.20 (m, 1H), 2.99 – 2.84 (m, 7H), 2.82 – 2.74 (m, 2H), 2.68 – 2.55 (m, 1H), 2.42 – 2.32 (m, 4H), 2.30 – 2.23 (m, 2H), 2.18 – 2.10 (m, 1H), 2.03 – 1.77 (m, 8H), 1.69 – 1.57 (m, 3H).			
A185	1H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 7.16 (d, J = 10.4 Hz, 1H), 7.13 – 7.04 (m, 3H), 7.00 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 6.8 Hz, 2H), 6.60 – 6.52 (m, 2H), 6.49 – 6.43 (m, 1H), 6.10 (d, J = 13.2 Hz, 1H), 5.65 (d, J = 8.4 Hz, 1H), 5.07 – 4.99 (m, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.37 – 4.31 (m, 1H), 4.26 (d, J = 16.8 Hz, 1H), 4.10 (d, J = 16.8 Hz, 1H), 3.99 – 3.91 (m, 1H), 3.86 – 3.77 (m, 3H), 3.73 – 3.65 (m, 2H), 3.24 – 3.10 (m, 3H), 2.97 – 2.82 (m, 8H), 2.77 – 2.65 (m, 1H), 2.62 – 2.54 (m, 1H), 2.44 – 2.32 (m, 4H), 2.31 – 2.24 (m, 2H), 2.21 – 2.06 (m, 2H), 2.00 – 1.90 (m, 1H), 1.89 – 1.80 (m, 2H), 1.74 (t, J = 10.8 Hz, 1H), 1.67 – 1.57 (m, 1H).	811.4	812.3	
A186	^{1}H NMR (400 MHz, MeOD) δ 7.39 (s, 1H), 7.11 (dd, *J* = 10.7, 4.8 Hz, 4H), 6.88 – 6.77 (m, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.66 – 6.57 (m, 3H), 6.51 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.32 (d, *J* = 8.6 Hz, 2H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.57 (s, 2H), 4.43 (t, *J* = 13.4 Hz, 2H), 4.18 (d, *J* = 5.0 Hz, 1H), 3.56 (d, *J* = 13.2 Hz, 3H), 3.38 (s, 2H), 3.00 (dd, *J* = 11.7, 5.9 Hz, 2H), 2.90 (dd, *J* = 15.5, 10.6 Hz, 1H), 2.77 (d, *J* = 15.4 Hz, 3H), 2.62 (t, *J* = 11.6 Hz, 2H), 2.47 (dt, *J* = 12.9, 8.3 Hz, 1H), 2.18 (dd, *J* = 13.2, 5.6 Hz, 5H), 1.99 (t, *J* = 17.1 Hz, 3H), 1.87 (d, *J* = 10.8 Hz, 3H), 1.76 (d, *J* = 7.2 Hz, 1H), 1.40 (d, *J* = 10.7 Hz, 2H).	750.4	751.3	
A187	1 H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1 H), 7.39 (d, J = 7.6 Hz, 1 H), 7.27 (d, J = 7.6 Hz, 1 H), 7.16-7.03 (m, 3 H), 6.76 (d, J = 6.0 Hz, 2 H), 6.64-6.52 (m, 2 H), 6.51-6.44 (m, 1 H), 6.25-6.14 (m, 2 H), 5.08 (dd, J = 13.2, 5.2 Hz, 1 H), 4.67 (d, J = 5.2 Hz, 1 H), 4.59-4.46 (m, 2 H), 4.43-4.17 (m, 2 H), 3.28-3.18 (m, 5 H), 3.00-2.83 (m, 8 H), 2.62-2.54	812.4	813.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	(m, 2 H), 2.43-2.31 (m, 3 H), 2.20-2.09 (m, 1 H), 2.03-1.85 (m, 5 H), 1.76-1.59 (m, 5 H), 1.47-1.24 (m, 5 H).			
A188	1 H NMR (400 MHz, DMSO-d6) δ 10.93 (s, 1 H), 9.15 (s, 1 H), 7.17-7.01 (m, 4 H), 6.93 (s, 1 H), 6.81-6.69 (m, 2 H), 6.64-6.51 (m, 2 H), 6.51-6.43 (m, 1 H), 6.25-6.14 (m, 2 H), 5.02 (dd, J = 13.2, 4.8 Hz, 1 H), 4.67 (d, J = 5.2 Hz, 1 H), 4.33-4.11 (m, 3 H), 3.95-3.87 (m, 1 H), 3.81 (d, J = 10.4 Hz, 1 H), 3.26-3.13 (m, 5 H), 3.00-2.84 (m, 8 H), 2.80-2.72 (m, 1 H), 2.62-2.54 (m, 2 H), 2.41-2.30 (m, 3 H), 2.21-2.02 (m, 2 H), 2.00-1.92 (m, 1 H), 1.77-1.59 (m, 4 H), 1.50-1.34 (m, 3 H), 1.33-1.21 (m, 2 H).	813.4	814.5	
A189	1 H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1 H), 8.29-8.14 (m, 1 H), 7.45 (s, 1 H), 7.13-6.98 (m, 4 H), 6.76 (d, J = 6.0 Hz, 2 H), 6.62-6.44 (m, 3 H), 6.26-6.14 (m, 2 H), 5.13-5.02 (m, 1 H), 4.67 (d, J = 5.2 Hz, 1 H), 4.46 (s, 2 H), 4.36-4.18 (m, 2 H), 3.28-3.19 (m, 5 H), 2.99-2.84 (m, 8 H), 2.63-2.56 (m, 2 H), 2.41-2.31 (m, 3 H), 2.20-2.09 (m, 1 H), 2.03-1.85 (m, 5 H), 1.77-1.60 (m, 5 H), 1.48-1.36 (m, 3 H), 1.32-1.21 (m, 2 H).	812.4	813.4	
A190	1 H NMR (400 MHz, DMSO-d6) δ 10.84 (s, 1 H), 8.83 (d, J = 8.4 Hz, 1 H), 8.37-8.17 (m, 1 H), 7.86 (d, J = 7.6 Hz, 1 H), 7.60 (d, J = 7.6 Hz, 1 H), 7.12-7.03 (m, 3 H), 6.75 (d, J = 6.0 Hz, 2 H), 6.64-6.43 (m, 3 H), 6.22-6.11 (m, 2 H), 4.79-4.64 (m, 2 H), 4.48 (s, 2 H), 3.27-3.21 (m, 2 H), 2.98-2.72 (m, 13 H), 2.41-2.36 (m, 2 H), 2.23-2.11 (m, 2 H), 2.04-1.82 (m, 7 H), 1.71-1.53 (m, 7 H), 1.46-1.38 (m, 2 H).	827.4	828.5	
A191	1 H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1 H), 7.46 (s, 1 H), 7.18-7.03 (m, 3 H), 6.98 (S, 1 H), 6.77 (d, J = 6.8 Hz, 2 H), 6.63-6.52 (m, 3 H), 6.51-6.34 (m, 2 H), 5.07 (dd, J = 13.2, 4.8 Hz, 1 H), 4.60 (d, J = 5.2 Hz, 1 H), 4.51-4.43 (m, 2 H), 4.37-4.18 (m, 2 H), 3.26-3.17 (m, 4 H), 3.00 (s, 3 H), 2.96-2.78 (m, 5 H), 2.65-2.54 (m, 3 H), 2.40-2.28 (m, 2 H),	798.4	799.5	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	2.20 (d, J = 6.4 Hz, 2 H), 2.04-1.85 (m, 5 H), 1.81-1.59 (m, 6 H), 1.30-1.17 (m, 2 H).			
A192	1H NMR (400 MHz, DMSO-d6)ppm: δ 10.94 (s, 1 H), 8.42 (s, 1 H), 7.13-7.19 (m, 4 H), 7.10 (d, J = 8.4 Hz, 1 H), 6.83 (d, J = 6.8 Hz, 2 H), 6.46-6.65 (m, 5 H), 6.20 (d, J = 8.4 Hz, 2 H), 5.00-5.05 (m, 1 H), 4.34-4.37 (m, 1 H), 4.24-4.28 (m, 1 H), 4.08-4.15 (m, 2 H), 3.94-3.99 (m, 1 H), 3.78-3.85 (m, 1 H), 3.14-3.23 (m, 4 H), 3.07 (s, 3 H), 2.89-2.99 (m, 5 H), 2.71-2.82 (m, 3 H), 2.64-2.69 (m, 1 H), 2.28-2.41 (m, 4 H), 2.04-2.16 (m, 2 H), 1.91-1.97 (m, 1 H), 1.66-1.75 (m, 5 H), 1.46-1.75 (m, 2 H).	795.4	796.4	
A193	1H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1 H), 8.40 (s, 1 H), 7.38 (d, J = 7.6 Hz, 1 H), 7.26 (d, J = 7.6 Hz, 1 H), 7.11-7.17 (m, 3 H), 6.82-6.83 (m, 2 H), 6.60-6.65 (m, 2 H), 6.53-6.56 (m, 2 H), 6.46-6.49 (m, 1 H), 6.20 (d, J = 8.8 Hz, 2 H), 5.06-5.10 (m, 1 H), 4.52 (s, 2 H), 4.38 (d, J = 17.2 Hz, 1 H), 4.21 (d, J = 17.2 Hz, 1 H), 4.10-4.13 (m, 1 H), 3.17-3.20 (m, 3 H), 3.07 (m, 3 H), 2.84-2.97 (m, 5 H), 2.30-2.35 (m, 2 H), 1.86-2.00 (m, 6 H), 1.64-1.75 (m, 6 H), 1.44-1.55 (m, 2 H), 1.20-1.29 (m, 5 H).	794.4	795.5	
A194	^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.25 (s, 1H), 7.15 – 7.06 (m, 4H), 7.03 (s, 1H), 6.84 (d, *J* = 6.8 Hz, 2H), 6.67 (dd, *J* = 14.5, 5.3 Hz, 2H), 6.52 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.06 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.35 – 4.26 (m, 4H), 4.05 – 3.91 (m, 2H), 3.51 – 3.42 (m, 2H), 3.40 – 3.33 (m, 4H), 3.17 (dd, *J* = 29.9, 11.1 Hz, 2H), 2.99 (ddd, *J* = 21.5, 13.9, 5.7 Hz, 3H), 2.90 – 2.83 (m, 1H), 2.76 (dd, *J* = 16.8, 3.5 Hz, 3H), 2.69 – 2.53 (m, 2H), 2.45 (ddd, *J* = 21.6, 12.7, 7.2 Hz, 2H), 2.22 (dd, *J* = 14.7, 9.2 Hz, 1H), 2.11 (dd, *J* = 17.3, 8.7 Hz, 3H), 1.84 (d, *J* = 7.3 Hz, 1H), 1.71 – 1.64 (m, 2H), 1.62 – 1.51 (m, 4H).	793.4	794.3	
A195	^{1}H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.27 (s, 1H), 7.16 – 7.06 (m, 4H), 6.85 (d, *J* = 6.9 Hz, 2H), 6.68 (dd, *J* = 13.1, 5.3 Hz, 2H), 6.52 (dd, *J* = 8.4,	793.4	794.3	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	2.5 Hz, 1H), 5.08 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.46 – 4.40 (m, 1H), 4.33 (dd, *J* = 19.1, 7.1 Hz, 3H), 4.25 (s, 1H), 4.14 (dd, *J* = 11.0, 7.1 Hz, 1H), 3.67 – 3.55 (m, 3H), 3.49 – 3.43 (m, 2H), 3.37 (d, *J* = 5.8 Hz, 3H), 3.19 (d, *J* = 7.6 Hz, 2H), 3.01 (ddd, *J* = 23.1, 17.1, 12.3 Hz, 3H), 2.90 – 2.71 (m, 3H), 2.55 – 2.41 (m, 2H), 2.22 – 2.10 (m, 3H), 1.85 (d, *J* = 7.4 Hz, 1H), 1.74 – 1.64 (m, 4H), 1.60 – 1.51 (m, 2H), 1.37 – 1.25 (m, 2H).			
A196	1H NMR (400 MHz, DMSO-d6) δ 10.92 (s, 1 H), 9.11 (s, 1 H), 7.07-7.11 (m, 3 H), 7.03 (s, 1 H), 6.93 (s, 1 H), 6.76 (d, J = 6.8 Hz, 2 H), 6.54-6.57 (m, 3 H), 6.44-6.47 (m, 1 H), 6.39 (d, J = 8.8 Hz, 1 H), 4.99-5.04 (m, 1 H), 4.59 (d, J = 5.2 Hz, 1 H), 4.22-4.29 (m, 2 H), 4.12-4.16 (m, 1 H), 3.86-3.91 (m, 1 H), 3.77-3.80 (m, 1 H), 3.12-3.16 (m, 1 H), 2.99 (s, 3 H), 2.83-2.89 (m, 5 H), 2.70-2.74 (m, 3 H), 2.55-2.60 (m, 1 H), 2.36-2.42 (m, 3 H), 2.27-2.34 (m, 2 H), 1.93-2.13 (m, 5 H), 1.62-1.74 (m, 5 H), 1.55-1.57 (m, 2 H), 1.41-1.45 (s, 3 H).	839.4	840.4	
A197	1H NMR (400 MHz, DMSO-d6) δ 10.92 (s, 1 H), 9.13 (s, 1 H), 7.17 (d, J = 8.0 Hz, 1 H), 7.07-7.11 (m, 3 H), 7.00 (d, J = 8.0 Hz, 1 H), 6.76 (d, J = 6.4 Hz, 2 H), 6.54-6.57 (m, 3 H), 6.38-6.47 (m, 2 H), 5.00-5.05 (m, 1 H), 4.59 (d, J = 4.8 Hz, 1 H), 4.24-4.36 (m, 2 H), 3.93-4.12 (m, 2 H), 3.80 (d, J = 11.2 Hz, 1 H), 3.13-3.21 (m, 2 H), 2.99 (s, 3 H), 2.83-2.92 (m, 6 H), 2.70-2.78 (m, 3 H), 2.33-2.45 (m, 4 H), 2.08-2.13 (m, 1 H), 1.88-2.01 (m, 4 H), 1.62-1.76 (m, 5 H), 1.56 (s, 2 H), 1.41-1.45 (m, 2 H), 1.24 (s, 1 H).	839.4	840.4	
A198	1 H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 7.26 (d, J = 7.6 Hz, 1 H), 7.17-7.04 (m, 3 H), 6.76 (d, J = 6.8 Hz, 2 H), 6.60-6.51 (m, 3 H), 6.47-6.35 (m, 2 H), 5.08 (dd, J = 13.2, 4.8 Hz, 1 H), 4.59 (d, J = 5.2 Hz, 1 H), 4.55-4.47 (m, 2 H), 4.41-4.33 (m, 1 H), 4.25-4.16 (m, 1 H), 3.29-3.23 (m, 2 H), 3.04-2.69 (m, 14 H), 2.62-2.54 (m, 1 H), 2.43-2.34 (m, 3 H), 2.32-2.24 (m, 1	838.4	839.8	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	H), 2.02-1.86 (m, 7 H), 1.72-1.61 (m, 5 H), 1.59-1.52 (m, 2 H), 1.46-1.38 (m, 2 H).			
A199	1 H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1 H), 7.45 (s, 1 H), 7.16-7.05 (m, 3 H), 7.00 (s, 1 H), 6.76 (d, J = 6.8 Hz, 2 H), 6.60-6.52 (m, 3 H), 6.48-6.36 (m, 2 H), 5.07 (dd, J = 13.2, 4.8 Hz, 1 H), 4.59 (d, J = 5.2 Hz, 1 H), 4.48-4.40 (m, 2 H), 4.36-4.18 (m, 2 H), 3.30-3.21 (m, 2 H), 3.01-2.72 (m, 13 H), 2.64-2.56 (m, 1 H), 2.42-2.34 (m, 3 H), 2.33-2.24 (m, 1 H), 2.00-1.83 (m, 7 H), 1.71-1.61 (m, 5 H), 1.59-1.52 (m, 2 H), 1.47-1.38 (m, 2 H).	838.4	839.8	
A200	1 H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1 H), 8.23 (s, 1 H), 7.42 (s, 1 H), 7.13-7.02 (m, 3 H), 6.75 (d, J = 6.4 Hz, 2 H), 6.62-6.53 (m, 2 H), 6.50-6.44 (m, 1 H), 6.25-6.12 (m, 2 H), 5.11-4.99 (m, 1 H), 4.70-4.63 (m, 1 H), 4.58-4.45 (m, 2 H), 4.37-4.15 (m, 2 H), 3.27-3.22 (m, 1 H), 3.01-2.70 (m, 13 H), 2.64-2.56 (m, 1 H), 2.43-2.36 (m, 3 H), 2.21-2.10 (m, 1 H), 2.01-1.87 (m, 7 H), 1.71-1.52 (m, 7 H), 1.46-1.38 (m, 2 H).	872.4	873.7	
A201	^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.37 (dd, *J* = 17.5, 7.7 Hz, 2H), 7.25 (d, *J* = 1.2 Hz, 1H), 7.10 (dt, *J* = 6.8, 4.6 Hz, 3H), 6.84 (d, *J* = 6.7 Hz, 2H), 6.67 (dd, *J* = 15.4, 5.4 Hz, 2H), 6.51 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.59 (s, 2H), 4.41 (q, *J* = 17.0 Hz, 2H), 4.29 (d, *J* = 5.6 Hz, 1H), 3.50 – 3.42 (m, 2H), 3.38 – 3.34 (m, 3H), 3.11 (d, *J* = 13.4 Hz, 2H), 3.06 – 2.96 (m, 2H), 2.92 – 2.83 (m, 1H), 2.81 – 2.72 (m, 3H), 2.70 – 2.58 (m, 1H), 2.55 – 2.38 (m, 4H), 2.18 – 2.07 (m, 5H), 1.86 (d, *J* = 8.4 Hz, 3H), 1.73 – 1.66 (m, 2H), 1.62 – 1.52 (m, 4H).	792.4	793.4	
A202	^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.37 (s, 1H), 7.25 (d, *J* = 1.2 Hz, 1H), 7.13 – 7.05 (m, 4H), 6.85 (d, *J* = 6.7 Hz, 2H), 6.67 (dd, *J* = 15.2, 5.4 Hz, 2H), 6.51 (dd, *J* = 8.3, 2.6 Hz, 1H), 5.11 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.55 (d, *J* = 16.4 Hz, 2H), 4.42 (t, *J* = 12.1 Hz, 2H), 4.29 (d, *J* = 5.8 Hz, 1H), 3.45 (s, 2H), 3.37 – 3.34 (m, 3H), 3.13 (s, 2H), 3.06 –	792.4	793.3	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	3.01 (m, 1H), 2.79 (s, 3H), 2.65 (d, *J* = 7.1 Hz, 1H), 2.55 – 2.42 (m, 4H), 2.09 (dd, *J* = 25.6, 14.7 Hz, 6H), 1.88 (d, *J* = 13.5 Hz, 3H), 1.69 (s, 2H), 1.58 (dd, *J* = 22.7, 7.5 Hz, 5H).			
A203	1 H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1 H), 7.17-7.03 (m, 4 H), 6.75 (d, J = 6.4 Hz, 2 H), 6.61-6.44 (m, 3 H), 6.23-6.13 (m, 2 H), 5.03 (dd, J = 13.2, 5.2 Hz, 1 H), 4.67 (d, J = 5.2 Hz, 1 H), 4.49-4.41 (m, 2 H), 4.31-4.11 (m, 2 H), 3.27-3.21 (m, 1 H), 3.03-2.66 (m, 13 H), 2.62-2.52 (m, 4 H), 2.48-2.32 (m, 4 H), 2.19-2.10 (m, 1 H), 2.04-1.82 (m, 7 H), 1.70-1.52 (m, 7 H), 1.47-1.39 (m, 2 H).	852.4	853.8	
A204	^{1}H NMR (400 MHz, MeOD) δ 8.51 (s, 2H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.09 – 6.95 (m, 3H), 6.79 (d, *J* = 7.8 Hz, 2H), 6.60 (dd, *J* = 10.0, 5.9 Hz, 2H), 6.50 (d, *J* = 8.2 Hz, 1H), 6.21 (d, *J* = 12.8 Hz, 1H), 6.02 (d, *J* = 7.5 Hz, 1H), 5.09 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.73 (d, *J* = 5.1 Hz, 1H), 4.42 (d, *J* = 9.1 Hz, 1H), 4.34 (t, *J* = 13.8 Hz, 2H), 4.24 – 4.10 (m, 2H), 3.68 (d, *J* = 32.3 Hz, 5H), 3.48 – 3.37 (m, 2H), 3.23 (s, 2H), 2.98 (dd, *J* = 17.8, 10.6 Hz, 5H), 2.91 – 2.69 (m, 2H), 2.54 – 2.36 (m, 2H), 2.34 – 2.15 (m, 2H), 2.08 (d, *J* = 32.4 Hz, 2H), 1.69 (s, 1H), 1.31 (d, *J* = 17.8 Hz, 4H).	785.4	786.3	
A205	^{1}H NMR (400 MHz, MeOD) δ 8.53 (s, 2H), 7.60 – 7.43 (m, 1H), 7.16 (d, *J* = 3.8 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 3H), 6.79 (d, *J* = 6.6 Hz, 2H), 6.61 (d, *J* = 11.1 Hz, 2H), 6.53 – 6.37 (m, 1H), 6.26 – 6.15 (m, 1H), 6.10 – 5.97 (m, 1H), 5.34 (t, *J* = 4.6 Hz, 1H), 5.13 (dd, *J* = 13.7, 5.1 Hz, 1H), 4.71 (d, *J* = 14.9 Hz, 1H), 4.62 (s, 2H), 4.50 – 4.36 (m, 2H), 3.70 (s, 2H), 3.62 (d, *J* = 13.5 Hz, 2H), 3.48 (s, 2H), 3.07 – 3.01 (m, 3H), 2.98 – 2.92 (m, 2H), 2.81 (t, *J* = 22.2 Hz, 2H), 2.39 (s, 3H), 2.22 – 2.17 (m, 2H), 2.03 (s, 4H), 1.64 (d, *J* = 26.2 Hz, 3H), 1.34 (s, 3H).	784.4	785.3	
A206	^{1}H NMR (400 MHz, MeOD) δ 8.54 (s, 1H), 7.57 – 7.41 (m, 2H), 7.12 – 7.00 (m, 3H), 6.79 (d, *J* = 7.2 Hz, 2H), 6.62 (dd, *J* = 7.6, 5.4 Hz, 2H), 6.47 (ddd, *J* = 17.5, 6.5, 2.4 Hz, 1H),	784.4	785.3	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	6.26 – 6.17 (m, 1H), 6.04 (dt, *J* = 14.0, 6.9 Hz, 1H), 5.19 – 5.09 (m, 1H), 4.77 – 4.65 (m, 3H), 4.43 (q, *J* = 17.1 Hz, 2H), 4.29 – 3.98 (m, 1H), 3.67 (dd, *J* = 38.2, 16.0 Hz, 5H), 3.47 (dd, *J* = 27.4, 13.8 Hz, 2H), 3.28 – 3.18 (m, 2H), 3.08 – 2.84 (m, 7H), 2.82 – 2.73 (m, 1H), 2.56 – 2.33 (m, 3H), 2.32 – 2.10 (m, 3H), 2.10 – 1.92 (m, 3H), 1.68 (d, *J* = 11.3 Hz, 1H), 1.36 – 1.22 (m, 1H).			
A212	1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1 H), 9.13 (s, 1 H), 8.15 (s, 1 H), 7.50-7.35 (m, 1 H), 7.15-7.03 (m, 3 H), 6.80-6.71 (m, 2 H), 6.61-6.53 (m, 2 H), 6.51-6.43 (m, 1 H), 6.24-6.14 (m, 2 H), 5.12-5.00 (m, 1 H), 4.67 (d, J = 5.2 Hz, 1 H), 4.62-4.50 (m, 2 H), 4.37-4.14 (m, 2 H), 3.29-3.14 (m, 5 H), 3.01-2.83 (m, 8 H), 2.64-2.55 (m, 2 H), 2.45-2.30 (m, 3 H), 2.22-1.89 (m, 6 H), 1.79-1.58 (m, 5 H), 1.50-1.35 (m, 3 H), 1.33-1.21 (m, 2 H).	846.4	847.4	
A213	1 H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1 H), 9.14 (s, 1 H), 7.15-7.04 (m, 4 H), 6.82-6.71 (m, 2 H), 6.62-6.53 (m, 2 H), 6.52-6.46 (m, 1 H), 6.25-6.15 (m, 2 H), 5.04 (dd, J = 13.2, 5.2 Hz, 1 H), 4.67 (d, J = 4.8 Hz, 1 H), 4.53-4.44 (m, 2 H), 4.34-4.10 (m, 2 H), 3.28-3.20 (m, 4 H), 3.03-2.83 (m, 9 H), 2.63-2.53 (m, 6 H), 2.43-2.34 (m, 1 H), 2.21-2.07 (m, 3 H), 1.99-1.86 (m, 3 H), 1.77-1.60 (m, 5 H), 1.51-1.36 (m, 3 H), 1.33-1.21 (m, 2 H).	826.4	827.8	
A214	1H NMR (400 MHz, DMSO-d6) δ 10.94 (s, 1 H), 8.16 (s, 1 H), 7.17-7.10 (m, 4 H), 6.83 (d, J = 7.2 Hz, 2 H), 6.65-6.59 (m, 2 H), 6.54-6.46 (m, 3 H), 6.19 (d, J = 8.4 Hz, 2 H), 5.03 (dd, J = 13.2, 5.2 Hz, 1 H), 4.49-4.41 (m, 2 H), 4.31-4.10 (m, 3 H), 2.98-2.91 (m, 4 H), 2.89-2.78 (m, 6 H), 2.61-2.53 (m, 5 H), 2.44-2.37 (m, 3 H), 2.01-1.84 (m, 7 H), 1.71-1.58 (m, 5 H), 1.51-1.38 (m, 4 H), 1.10 (s, 1 H).	804.4	805.8	
A216	1 H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1 H), 8.27 (s, 1 H),7.67-7.48 (m, 1 H), 7.36-7.23 (m, 1 H), 7.15-7.05 (m, 5 H), 6.78 (d, J = 6.8 Hz, 3 H), 6.62-6.40 (m, 4 H), 6.10 (d, J = 13.6 Hz, 1 H), 5.68 (d, J = 8.4 Hz, 1 H), 5.09-4.96 (m, 1 H), 4.64-4.59 (m, 1 H), 4.50-4.42	852.4	853.8	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	(m, 2 H), 4.33-4.25 (m, 1 H), 4.19-4.11 (m, 1 H), 3.55-3.48 (m, 5 H), 3.24-3.20 (m, 2 H), 2.93-2.92 (m, 3 H), 2.88-2.84 (m, 1 H), 2.83-2.75 (m, 3 H), 2.55-2.53 (m, 3 H), 2.12-2.08 (m, 2 H), 1.93-1.85 (m, 6 H), 1.71-1.62 (m, 5 H), 1.46-1.40 (m, 2 H), 0.92-0.87 (m, 1 H).			
A217	1 H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1 H), 8.23 (s, 1 H), 7.42 (s, 1 H), 7.13-7.04 (m, 3 H), 6.79-6.71 (m, 2 H), 6.63-6.53 (m, 2 H), 6.51-6.42 (m, 1 H), 6.25-6.14 (m, 2 H), 5.04 (dd, J = 13.2, 5.2 Hz, 1 H), 4.67 (d, J = 5.2 Hz, 1 H), 4.62-4.53 (m, 2 H), 4.36-4.28 (m, 1 H), 4.22-4.15 (m, 1 H), 3.28-3.20 (m, 3 H), 3.05-2.80 (m, 9 H), 2.63-2.55 (m, 2 H), 2.42-2.31 (m, 3 H), 2.20-2.10 (m, 1 H), 2.02-1.85 (m, 5 H), 1.78-1.60 (m, 5 H), 1.47-1.24 (m, 5 H).	846.4	847.3	
A218	1 H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1 H), 8.21 (s, 1 H), 7.41 (s, 1 H), 7.11-7.03 (m, 3 H), 6.75 (d, J = 6.0 Hz, 2 H), 6.61-6.52 (m, 2 H), 6.50-6.44 (m, 1 H), 6.23-6.13 (m, 2 H), 5.09-4.99 (m, 1 H), 4.67 (d, J = 5.2 Hz, 1 H), 4.59-4.50 (m, 2 H), 4.35-4.29 (m, 1 H), 4.22-4.16 (m, 1 H), 3.28-3.21 (m, 1 H), 3.04-2.66 (m, 13 H), 2.63-2.55 (m, 1 H), 2.47-2.29 (m, 4 H), 2.19-2.09 (m, 1 H), 2.05-1.84 (m, 7 H), 1.74-1.63 (m, 4 H), 1.59-1.52 (m, 2 H), 1.48-1.38 (m, 2 H).	872.4	873.8	
A219	1 H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1 H), 7.23 (s, 1 H), 7.13-7.00 (m, 3 H), 6.75 (d, J = 6.4 Hz, 2 H), 6.62-6.51 (m, 2 H), 6.50-6.40 (m, 1 H), 6.25-6.10 (m, 2 H), 5.02 (dd, J = 13.2, 5.2 Hz, 1 H), 4.67 (d, J = 4.8 Hz, 1 H), 4.43 (s, 2 H), 4.29-4.10 (m, 2 H), 3.27-3.21 (m, 2 H), 3.00-2.71 (m, 13 H), 2.64-2.56 (m, 1 H), 2.45-2.34 (m, 6 H), 2.19-2.10 (m, 1 H), 2.03-1.82 (m, 7 H), 1.70-1.54 (m, 7 H), 1.46-1.38 (m, 2 H).	852.4	853.8	
A220	1 H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1 H), 8.23 (s, 1 H), 7.23 (s, 1 H), 7.16-7.01 (m, 3 H), 6.75 (d, J = 6.4 Hz, 2 H), 6.61-6.52 (m, 2 H), 6.50-6.45 (m, 1 H), 6.24-6.11 (m, 2 H), 5.02 (dd, J = 13.2, 5.2 Hz, 1 H), 4.66 (d, J = 5.2 Hz, 1 H), 4.47-4.39 (m, 2 H), 4.29-4.12	852.4	853.8	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	(m, 2 H), 3.27-3.22 (m, 1 H), 3.00-2.71 (m, 13 H), 2.61-2.55 (m, 1 H), 2.44-2.33 (m, 6 H), 2.21-2.11 (m, 1 H), 2.03-1.82 (m, 7 H), 1.69-1.52 (m, 7 H), 1.47-1.38 (m, 2 H).			
A221	1H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.24 (s, 1H), 7.29 (s, 1H), 7.11 – 7.02 (m, 3H), 6.78 – 6.71 (m, 2H), 6.59 – 6.53 (m, 2H), 6.50 – 6.43 (m, 1H), 6.24 – 6.13 (m, 2H), 5.11 – 5.01 (m, 1H), 4.66 (d, J = 5.6 Hz, 1H), 4.43 (t, J = 10.4 Hz, 1H), 4.36 – 4.24 (m, 2H), 4.18 (d, J = 17.6 Hz, 1H), 3.45 – 3.43 (m, 1H), 3.26 – 3.16 (m, 3H), 3.00 – 2.92 (m, 5H), 2.90 – 2.81 (m, 5H), 2.80 – 2.69 (m, 3H), 2.61 – 2.53 (m, 1H), 2.47 – 2.42 (m, 2H), 2.39 – 2.28 (m, 3H), 2.19 – 2.11 (m, 1H), 2.01 – 1.91 (m, 3H), 1.72 – 1.54 (m, 5H), 1.45 – 1.40 (m, 2H).	873.3	874.2	
A222	1 H NMR (400 MHz, DMSO-d6) δ 10.93 (s, 1 H), 8.18 (s, 1 H), 7.12-7.00 (m, 4 H), 6.79-6.71 (m, 2 H), 6.61-6.54 (m, 2 H), 6.49-6.45 (m, 1 H), 6.24-6.14 (m, 2 H), 4.99 (dd, J = 13.2, 5.2 Hz, 1 H), 4.67 (d, J = 5.2 Hz, 1 H), 4.49-4.40 (m, 2 H), 4.29-4.21 (m, 1 H), 4.16-4.05 (m, 1 H), 3.83-3.79 (m, 3 H), 2.97-2.71 (m, 13 H), 2.43-2.31 (m, 4 H), 2.19-2.09 (m, 1 H), 1.99-1.89 (m, 7 H), 1.72-1.51 (m, 8 H), 1.49-1.36 (m, 3 H).	868.4	869.8	
A223	1 H NMR (400 MHz, DMSO-d6) δ 10.93 (s, 1 H), 8.24 (s, 1 H), 7.13-7.00 (m, 4 H), 6.82-6.70 (m, 2 H), 6.61-6.45 (m, 3 H), 6.25-6.11 (m, 2 H), 4.99 (dd, J = 13.2, 5.2 Hz, 1 H), 4.67 (d, J = 5.2 Hz, 1 H), 4.49-4.41 (m, 2 H), 4.29-4.23 (m, 1 H), 4.12-4.06 (m, 1 H), 3.82 (s, 3 H), 3.27-3.21 (m, 1 H), 2.98-2.75 (m, 13 H), 2.44-2.35 (m, 3 H), 2.19-2.09 (m, 1 H), 2.01-1.91 (m, 7 H), 1.72-1.52 (m, 8 H), 1.49-1.37 (m, 2 H).	868.4	869.8	
A224	1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.29 – 8.28 (m, 2H), 7.30 (s, 1H), 7.11 – 7.06 (m, 3H), 6.77 – 6.75 (m, 2H), 6.60 – 6.55 (m, 2H), 6.49 – 6.47 (m, 1H), 6.21 – 6.17 (m, 2H), 5.08 – 5.03 (m, 1H), 4.68 – 4.66 (m, 1H), 4.48 – 4.42 (m, 1H), 4.36 – 4.29 (m, 2H), 4.21 – 4.20 (m, 1H), 3.69 – 3.64 (m,	847.4	848.3	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	2H), 3.02 – 2.98 (m, 2H), 2.95 (s, 3H), 2.91 – 2.81 (m, 3H), 2.67 – 2.60 (m, 3H), 2.46 – 2.40 (m, 2H), 2.36 – 2.24 (m, 3H), 2.18 – 2.13 (m, 1H), 1.75 – 1.70 (m, 2H), 1.63 – 1.62 (m, 1H), 1.45 – 1.37 (m, 3H), 1.32 – 1.24 (m, 3H).			
A225	1H NMR (400 MHz, DMSO-d6) δ 10.92 (s, 1 H), 9.13 (s, 1 H), 8.15-7.07 (m, 3 H), 7.02 (s, 1 H), 6.77-6.75 (d, J=8 Hz, 2 H), 6.59-6.55 (m, 2 H), 6.49-6.46 (m, 1 H), 6.21-6.18 (m, 2 H), 5.02-4.97 (dd, J = 4 Hz, J =12 Hz, 1 H), 4.68-4.67 (d, J =4 Hz 1 H), 4.49-4.44 (m, 2 H), 4.29-4.08 (m, 2H), 3.82 (s, 3 H), 3.24 (s, 5 H), 2.96 (s, 3 H), 2.90-2.85 (m, 4 H), 2.62-2.55 (m, 2 H), 2.42-2.32 (m, 3 H), 2.18-2.13 (m, 1 H), 2.01-1.92 (m, 5 H), 1.75-1.62 (m, 5 H), 1.43-1.40 (m, 3 H), 1.27-1.24 (m, 2 H).	842.4	843.3	
A226	1H NMR (400 MHz, MeOD-d4) δ 7.05-7.08 (m, 3 H), 6.94 (s, 1 H), 6.75-6.77 (d, J = 7.6 Hz, 2 H), 6.60-6.64 (m, 2 H), 6.50-6.53 (d, J = 10.4 Hz, 1 H), 6.19-6.29 (m, 3 H), 5.05-5.10 (dd, J = 13.2 Hz, 5.2 Hz, 1 H), 4.76-4.78 (d, J = 8.8 Hz, 2 H), 4.57 (s, 2 H), 4.28-4.39 (m, 2 H), 3.91 (s, 3 H), 3.24-3.35 (m, 3 H), 3.01 (s, 5 H), 2.85-2.96 (m, 4 H), 2.58-2.83 (m, 5 H), 2.11-2.20 (m, 5 H), 1.91-1.95 (d, J = 13.2 Hz, 2 H), 1.79-1.84 (m, 2 H), 1.67-1.70 (m, 3 H), 1.46 (s, 3 H).	842.4	843.5	
A227	1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1 H), 9.13 (s, 1 H), 7.06-7.16 (m, 4 H), 6.73-6.79 (m, 2 H), 6.51-6.61 (m, 2 H), 6.47 (dd, J = 8.4 Hz, 2.0 Hz, 1 H), 6.19 (dd, J = 10.0 Hz, 2.0 Hz, 2 H), 5.00-5.08 (m, 1 H), 4.65-4.69 (m, 1 H), 4.43-4.51 (m, 2 H), 4.29 (d, J = 16.8 Hz, 1 H), 4.14 (d, J = 16.8 Hz, 1 H), 3.65-3.72 (m, 1 H), 3.20-3.28 (m, 3 H), 2.74-3.03 (m, 13 H), 2.59-2.63 (m, 1 H), 2.27-2.45 (m, 2 H), 2.05-2.22 (m, 4 H), 1.83-2.03 (m, 5 H), 1.53-1.81 (m, 8 H), 1.43-1.52 (m, 1 H), 1.29-1.41 (m, 2 H).	882.4	883.1	
A228	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.27 – 8.99 (m, 1H), 7.16 – 7.02 (m, 4H), 6.82 – 6.71 (m, 2H), 6.62 – 6.53 (m, 2H), 6.49 – 6.44 (m, 1H), 6.22 – 6.14 (m, 2H),	853.4	854.4	

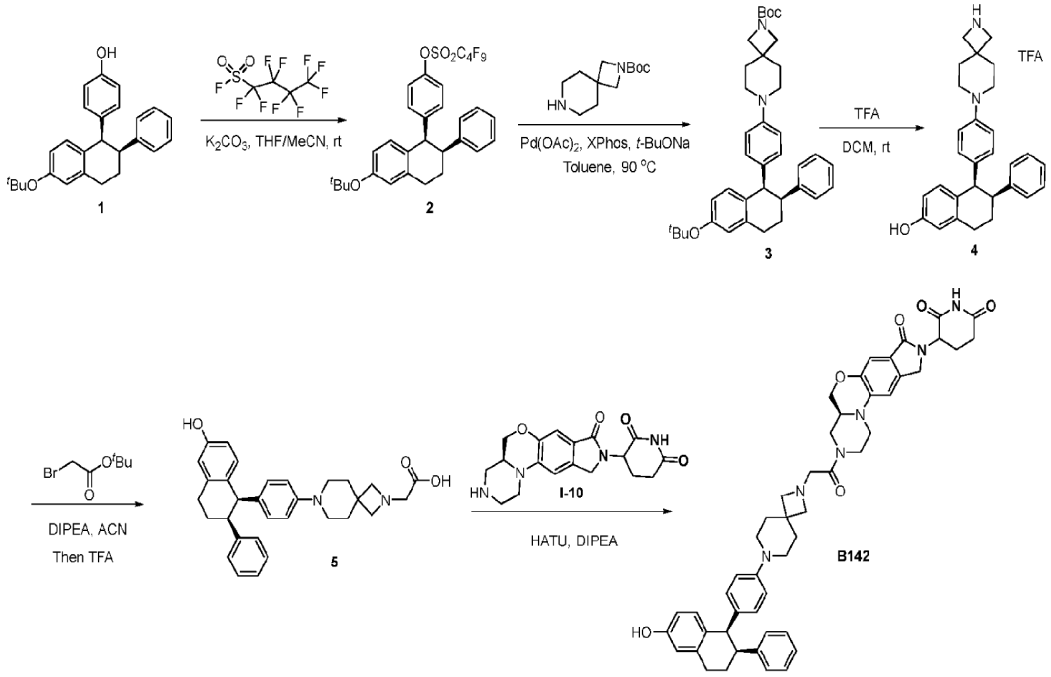
Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	5.08 – 4.99 (m, 1H), 4.66 (d, J = 5.2 Hz, 1H), 4.44 (t, J = 10.4 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.21 – 4.08 (m, 2H), 3.28 – 3.20 (m, 2H), 3.16 – 3.06 (m, 2H), 3.01 – 2.94 (m, 4H), 2.92 – 2.81 (m, 5H), 2.79 – 2.68 (m, 4H), 2.62 – 2.55 (m, 1H), 2.47 – 2.36 (m, 4H), 2.33 – 2.24 (m, 4H), 2.18 – 2.10 (m, 1H), 2.00 – 1.89 (m, 3H), 1.72 – 1.53 (m, 5H), 1.48 – 1.33 (m, 2H).			
A229	1H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 9.13 (s, 1H), 7.12 – 7.04 (m, 4H), 6.81 – 6.71 (m, 2H), 6.60 – 6.54 (m, 2H), 6.50 – 6.44 (m, 1H), 6.25 – 6.11 (m, 2H), 5.11 – 5.00 (m, 1H), 4.67 (d, J = 5.2 Hz, 1H), 4.46 (t, J = 10.4 Hz, 1H), 4.32 – 4.25 (m, 1H), 4.24 – 4.18 (m, 1H), 4.16 – 4.08 (m, 1H), 3.29 – 3.07 (m, 6H), 3.03 – 2.94 (m, 5H), 2.91 – 2.70 (m, 4H), 2.62 – 2.54 (m, 2H), 2.47 – 2.35 (m, 3H), 2.33 – 2.13 (m, 6H), 1.99 – 1.93 (m, 1H), 1.77 – 1.57 (m, 3H), 1.46 – 1.21 (m, 5H).	827.4	828.3	
A230	1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.30 (s, 1H), 7.14 – 7.07 (m, 4H), 6.75 (d, J = 7.60 Hz, 2H),6.59 – 6.55 (m, 2H), 6.46 (d, J = 10.40 Hz, 1H), 6.21 – 6.18 (m, 2H), 5.04 – 5.01 (m, 1H), 4.68 – 4.67 (m, 1H), 4.49 – 4.44 (m, 2H), 4.29 (d, J = 17.20 Hz, 1H), 4.14 (d, J = 16.80 Hz, 1H),3.70 – 3.67 (m, 1H), 3.28 – 3.23 (m, 3H), 2.99 (s, 5H), 2.91 – 2.84 (m, 3H), 2.77 – 2.74 (m, 2H), 2.67 – 2.60 (m, 1H), 2.54 (s, 3H), 2.45 – 2.33 (m, 2H), 2.19 – 2.11 (m, 4H), 1.96 – 1.88 (m, 5H), 1.81 – 1.76 (m, 1H), 1.67 – 1.60 (m, 7H), 1.50 – 1.43 (m, 1H), 1.36 – 1.34 (m, 2H).	882.4	883.3	
A231	1 H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1 H), 9.10 (s, 1 H), 7.43 (s, 1 H), 7.20-7.06 (m, 3 H), 6.83 (d, J = 6.4 Hz, 2 H), 6.67-6.58 (m, 2 H), 6.57-6.43 (m, 3 H), 6.20 (d, J = 8.4 Hz, 2 H), 5.05 (dd, J = 13.2, 5.2 Hz, 1 H), 4.59-4.48 (m, 2 H), 4.37-4.28 (m, 1 H), 4.23-4.10 (m, 2 H), 3.70-3.63 (m, 1 H), 3.17-3.10 (m, 2 H), 3.03-2.74 (m, 8 H), 2.63-2.55 (m, 2 H), 2.43-2.34 (m, 1 H), 2.22-2.08 (m, 3 H),	854.4	855.2	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	2.04-1.86 (m, 6 H), 1.76-1.52 (m, 8 H), 1.44-1.28 (m, 3 H).			
A232	1 H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1 H), 8.19 (s, 1 H), 7.46-7.37 (m, 1 H), 7.14-7.03 (m, 3 H), 6.80-6.62 (m, 2 H), 6.62-6.52 (m, 2 H), 6.51-6.45 (m, 1 H), 6.27-6.15 (m, 2 H), 5.05 (dd, J = 13.2, 5.2 Hz, 1 H), 4.67 (d, J = 5.2 Hz, 1 H), 4.58-4.49 (m, 2 H), 4.40-4.30 (m, 1 H), 4.25-4.15 (m, 1 H), 3.71-3.66 (m, 1 H), 3.28-3.23 (m, 2 H), 3.02-2.83 (m, 11 H), 2.81-2.72 (m, 2 H), 2.64-2.57 (m, 1 H), 2.45-2.36 (m, 1 H), 2.22-2.10 (m, 3 H), 2.01-1.87 (m, 5 H), 1.77-1.55 (m, 8 H), 1.50-1.29 (m, 3 H).	902.4	903.2	
A233	1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1 H), 9.11 (s, 1 H), 7.43 (s, 1 H), 7.16-7.11 (m, 3 H), 6.83-6.82 (d, J = 4 Hz, 2 H), 6.66-6.60 (m, 2 H), 6.54-6.47 (m, 3 H), 6.21-6.19 (d, 2 H), 5.07-5.03 (dd, J = 4 Hz, 12 Hz, 1 H), 4.54 (s, 2 H), 4.36-4.16 (m, 2 H), 4.13-4.12 (m, 1 H), 3.68-3.65 (m, 2 H), 3.17 (s, 6 H), 3.01-2.75 (m, 6 H), 2.19-2.13 (m, 2 H), 2.07-1.90 (m, 6 H), 1.72-1.62 (m, 5 H), 1.59-1.52 (m, 3 H), 1.34-1.24 (m, 4 H).	854.4	855.4	
A234	1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1 H), 9.11 (s, 1 H), 7.42 (s, 1 H), 7.11-7.05 (m, 3 H), 6.77 (d, J = 8.0 Hz, 2 H), 6.59-6.55 (m, 2 H), 6.49-6.46 (m, 1 H), 6.21-6.18 (m, 2 H), 5.07-5.03 (m, 1 H), 4.68 (, 1 H), 4.57-4.52 (m, 2 H), 4.36-4.15 (m, 2 H), 3.69-3.67 (m, 1 H), 3.96 (s, 3 H), 2.83-2.75 (m, 8 H), 2.67-2.56 (m, 1 H), 2.36-2.23 (m, 3 H), 2.18-2.13 (m, 5 H), 1.94-1.89 (m, 5 H), 1.76-1.56 (m, 9 H), 1.39-1.30 (m, 2 H).	902.4	903.3	
A235	1 H NMR (400 MHz, DMSO-d6) δ 10.92 (s, 1 H), 8.31 (s, 1 H), 7.19-7.08 (m, 3 H), 7.01 (s, 1 H), 6.83 (d, J = 6.8 Hz, 2 H), 6.68-6.59 (m, 2 H), 6.56-6.43 (m, 3 H), 6.20 (d, J = 8.4 Hz, 2 H), 4.99 (dd, J = 13.2, 4.8 Hz, 1 H), 4.52-4.40 (m, 2 H), 4.31-4.20 (m, 1 H), 4.15-4.06 (m, 2 H), 3.82 (s, 3 H), 3.69-3.65 (m, 1 H), 3.31-3.22 (m, 3 H), 3.16-3.10 (m, 2 H), 2.97-2.83 (m, 5 H), 2.81-2.71 (m, 2 H), 2.64-2.55 (m, 1 H), 2.40-2.31 (m, 1 H), 2.20-2.12	850.4	851.7	

Compound No.	^{1}H NMR	Calcd. $(M+H)^+$	Found $(M+H)^+$	LCMS method
	(m, 2 H), 2.04-1.87 (m, 6 H), 1.75-1.50 (m, 8 H), 1.45-1.37 (m, 1 H), 1.37-1.24 (m, 2 H).			
A236	1 H NMR (400 MHz, DMSO-d6) δ 10.92 (s, 1 H), 8.25 (s, 1 H), 7.18-7.08 (m, 3 H), 7.01 (s, 1 H), 6.83 (d, J = 6.8 Hz, 2 H), 6.73-6.58 (m, 2 H), 6.56-6.43 (m, 3 H), 6.20 (d, J = 8.4 Hz, 2 H), 4.99 (dd, J = 13.2, 5.2 Hz, 1 H), 4.50-4.38 (m, 2 H), 4.32-4.23 (m, 1 H), 4.14-4.07 (m, 2 H), 3.82 (s, 3 H), 3.66-3.65 (m, 1 H), 3.30-3.21 (m, 3 H), 3.17-3.11 (m, 2 H), 2.98-2.83 (m, 5 H), 2.80-2.73 (m, 2 H), 2.62-2.54 (m, 1 H), 2.39-2.31 (m, 1 H), 2.20-2.13 (m, 2 H), 2.05-1.87 (m, 6 H), 1.77-1.51 (m, 8 H), 1.45-1.38 (m, 1 H), 1.36-1.26 (m, 2 H).	850.4	851.7	

FOR "B" COMPOUNDS

Compound B142: 3-((S)-3-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



Step 1: 4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl 4,4,4,4,4,4,4,4,4-nonafluoro-4l12-buta-1,3-diyne-1-sulfonate

[0792] To a solution of **1** (2.0 g, 1 eq) and 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (3.24 g, 2.0 eq) in tetrahydrofuran (10 mL) and acetonitrile (10 mL) was added potassium carbonate (2.6 g, 3.5 eq). The reaction mixture was stirred at rt for 16 hours. TLC (petroleum ether : ethyl acetate = 10 : 1) indicated the starting material was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (petroleum ether:ethyl acetate=100:0 to 95:5). The desired compound **2** (3.5 g, > 99% yield) was obtained as a colorless oil. ^{1}H NMR (400 MHz, CDCl3) δ 7.21-7.11 (m, 3H), 6.94-6.86 (m, 3H), 6.84-6.73 (m, 4H), 6.46 (d, J=8.8 Hz, 2H), 4.33 (d, J=5.2 Hz, 1H), 3.50-3.40 (m, 1H), 3.16-2.95 (m, 2H), 2.20-2.02 (m, 1H), 1.91-1.79 (m, 1H), 1.38 (s, 9H).

Step 2: tert-butyl 9-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[3.5]undecane-3-carboxylate

[0793] A mixture of **2** (500 mg, 1.0 eq), *tert*-butyl 3,9-diazaspiro[3.5]undecane-3-carboxylate (345 mg, 2.0 eq), $Pd(OAc)_2$ (73 mg, 0.15 eq), XPhos (73 mg, 0.2 eq) and *t*-BuONa (257 mg, 3.5 eq) in tolune (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 90 °C for 16 h under N_2 atmosphere. LC-MS showed one main peak with desired MS was detected. TLC (PE:EA = 10:1) indicated the starting material was consumed completely, and a new spot formed. The mixture was cooled, diluted with EA, filtered through Celite, the filter cake was washed with EA. The filtrate was concentrated. The residue was purified by silica gel flash chromatography (PE:EA = 100:0 to 85:15). The desired product **3** (350 mg, 79% yield) was obtained as a colorless oil. LCMS (ESI) m/z: 581.17 [M+1].

Step 3: (5R,6S)-5-(4-(3,9-diazaspiro[3.5]undecan-3-yl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol trifluoroacetate salt

[0794] To a solution of **3** (350 mg) in DCM (5 mL) was added TFA (2.5 mL). The reaction mixture was stirred overnight, then concentrated under reduced pressure. The residue was lyophilized, and compound **4** (333 mg) was obtained as a white solid. LCMS (ESI) m/z: 425.10 [M+1].

Step 4: 2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetic acid

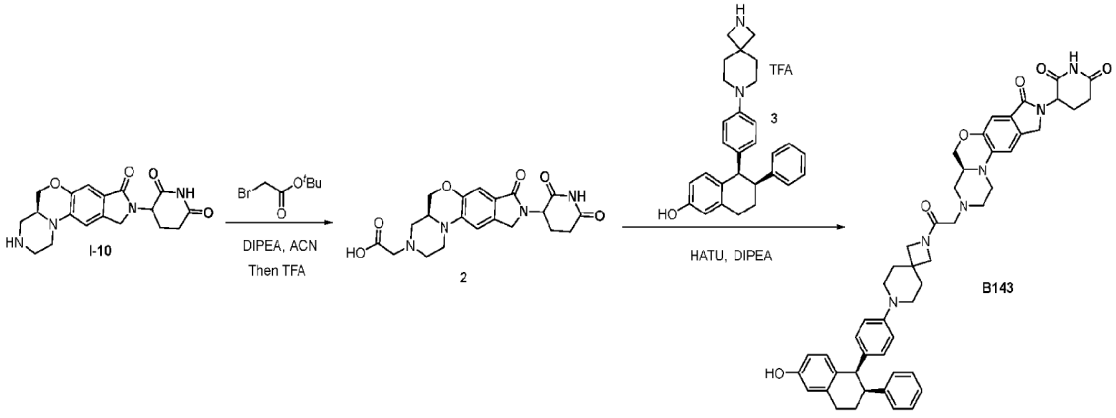
[0795] To a solution of **4** (30 mg, 1.0 equiv) in acetonitrile (6 mL) was added DIPEA (77.5 uL, 8.0 equiv) and tert-butyl 2-bromoacetate (9 uL, 1.1 equiv). The reaction mixture was stirred overnight. Then the solvent was removed, and the residue was purified by pre-HPLC. The fraction

containing product was concentrated, followed by adding TFA. 2 h Later, TFA was removed under reduced pressure and compound **5** was obtained as a white solid after lyophilization. LCMS (ESI) m/z: 483.31 [M+l].

*Step 5: 3-((S)-3-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (**B142**)*

[0796] To a solution of **5** (12 mg, 1.0 equiv) in DMF (2.0 mL) was added DIPEA (21 uL, 6.0 equiv) and HATU (7.6 mg, 1.0 equiv). 10 Min later, intermediate **1-10** (11.3 mg, 1.2 equiv) was added and the reaction mixture was stirred for 10-15 min. Then the reaction mixture was inmediately purified by pre-HPLC to obtain the title compound **B142** as a white solid 14.2 mg (yield = 69.6%). LC-MS (ESI) m/z: 821.36 [M+l].

Compound B143: 3-((S)-3-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



Step 1: 2-((4aS)-9-(2,6-dioxopiperidin-3-yl)-8-oxo-1,2,4a,5,9,10-hexahydro-8H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-3(4H)-yl)acetic acid

[0797] To a solution of **1** (50 mg, 1.0 equiv) in acetonitrile (6 mL) was added DIPEA (148 uL, 8.0 equiv) and tert-butyl 2-bromoacetate (17.2 uL, 1.1 equiv). The reaction mixture was stirred overnight. Then the solvent was removed, and the residue was purified by pre-HPLC. The fraction containing product was concentrated, followed by adding TFA. 2 h Later, TFA was removed under

reduced pressure and compound **2** was obtained as a white solid (45 mg, yiled = 80.4%) after lyophilization. LC-MS (ESI) m/z: 415.16 [M+l].

Step 2: 3-((S)-3-(2-(7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

[0798] To a solution of **2** (14 mg, 1.0 equiv) in DMF (2.0 mL) was added DIPEA (27.7 uL, 6.0 equiv) and HATU (10.1mg, 1.0 equiv). 10 Min later, compound **2** (17.1 mg, 1.2 equiv) was added and the reaction mixture was stirred for 10-15 min. Then the reaction mixture was inmediately purified by pre-HPLC to obtain the title compound **B143** as a white solid 24 mg (yield = 97%). LCMS (ESI) m/z: 821.36 [M+l].

[0799] The following compounds were prepared in a manner analogous to compounds **B142** and **B143**.

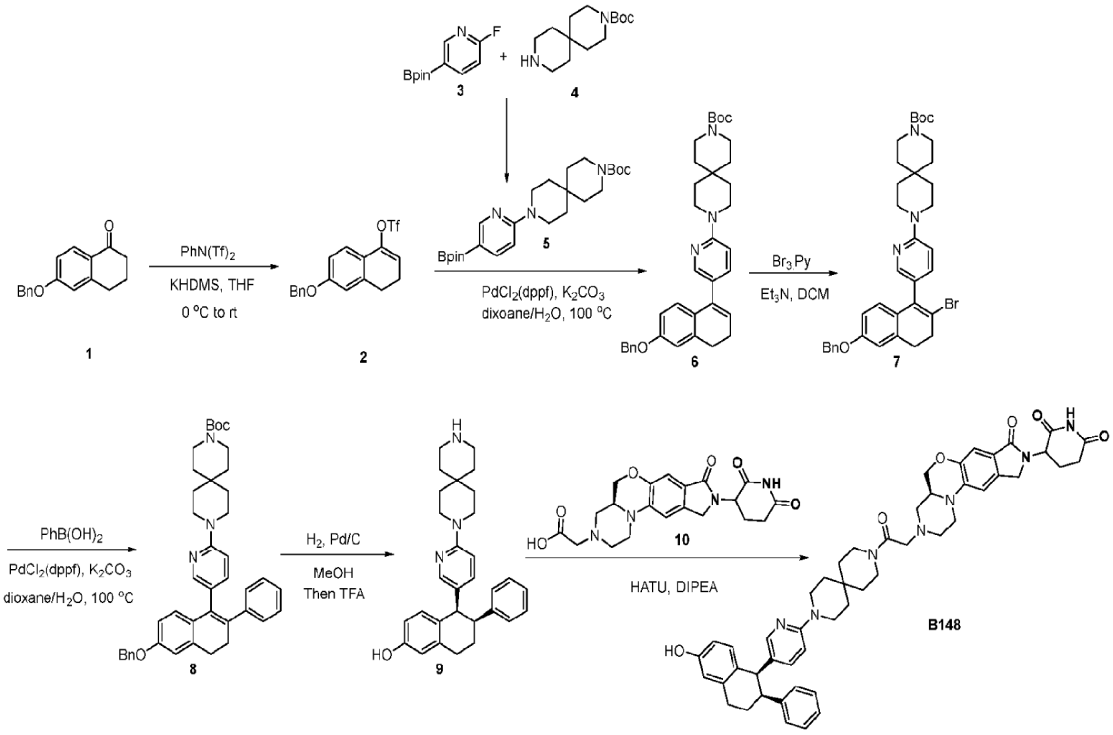
Table 5. Compounds Prepared According to Compounds B142 and B143.

Compound No.	LC-MS $(M+H)^+$
B142	821.36
B143	821.51
B144	781.47
B145	781.27
B146	849.46
B147	849.45
B152	807.35
B153	807.38
B154	807.40
B155	807.34
B156	807.36
B157	807.34
B160	821.35
B161	821.37
B162	834.41
B168	806.20

Compound No.	LC-MS $(M+H)^+$
B169	806.22
B170	806.34
B171	820.18
B172	808.15
B204	767.3
B205	793.32
B206	807.38
B207	767.31
B208	793.41
B209	807.4
B212	806.4
B213	820.49
B214	820.33
B218	821.39
B219	821.39
B220	767.35
B221	821.39
B222	793.36
B223	823.41
B244	781.3
B245	767.9
B246	768.3
B247	780.8
B248	768.3
B249	781.3
B250	767.30
B251	793.20
B252	821.20

Compound No.	LC-MS $(M+H)^+$
B253	820.30
B254	821.30

Compound B148: 3-((S)-3-(2-(9-(5-(cis-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



Step 1: 6-(benzyloxy)-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate

[0800] To a solution of **1** (12.6 g, 1.0 equiv) and $PhN(Tf)_2$ (21.4 g, 1.2 equiv) in THF (180 mL) was added KHDMS (0.5 M in toluene, 150 mL, 1.5 equiv) dropwise at 0 °C. After the addition was completed, the reaction was warmed to rt and kept stirring for 4 h. Then quenched with ice water (150 mL) under ice bath. The result mixture was extracted with EA, and the combined EA layers was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel flash chromatography to give compound **2** as a light-yellow oil (15.1 g, yield = 79%).

Step 2: tert-butyl 9-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0801] To a solution of **3** (1.0 g, 1.0 equiv) and **4** (1.37 g, 1.2 equiv) in DMSO (10 mL) was added DIPEA (2.0 mL, 2.5 equiv). The reaction mixture was stirred at 100 °C overnight. Then the reaction mixture was cooled to rt, diluted with EA, washed with brine and concentrated to give a crude product, which was purified by silica gel flash chromatography to give compound **5** as a white powder (1.04 g, yield = 51%). LC-MS (ESI) m/z: 376.32 [M+1].

Step 3: tert-butyl 9-(5-(6-(benzyloxy)-3,4-dihydronaphthalen-1-yl)pyridin-2-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0802] A mixture of **2** (381 mg, 1.0 equiv), **5** (500 mg, 1.1 equiv), $PdCl_2dppf$ (160 mg, 0.2 equiv) and K_2CO_3 (377 mg, 2.5 equiv) in dioxane/H_2O (8 mL/2 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 100 °C for 3 h under N_2 atmosphere. LC-MS showed one main peak with desired MS was detected. The reaction mixture was cooled to rt, extracted with EA, washed with brine, dried over Na_2SO_4 and concentrated. The result residue was purified by silica gel flash chromatography to give compound **6** as a white powder (1.04 g, yield = 51%). LC-MS (ESI) m/z: 376.32 [M+1].

Step 4: tert-butyl 9-(5-(6-(benzyloxy)-2-bromo-3,4-dihydronaphthalen-1-yl)pyridin-2-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0803] To a solution of **6** (270 mg, 1.0 equiv) in DCM (25 mL) was added Et_3N (134 uL, 2.0 equiv), followed by adding $Br_3.Py$ (137 mg, 0.9 equiv) in potionwise at 0 °C. The reaction mixture was kept stirring for 1 h, then diluted with DCM, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel flash chromatography to give compound **7** as a colorless oil (194 mg, yield = 63%). LC-MS (ESI) m/z: 644.05 [M+1].

Step 5: tert-butyl 9-(5-(6-(benzyloxy)-2-phenyl-3,4-dihydronaphthalen-1-yl)pyridin-2-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0804] A mixture of **7** (194 mg, 1.0 equiv), $PhB(OH)_2$ (73.5 mg, 2.0 equiv), $PdCl_2dppf$ (44 mg, 0.2 equiv) and K_2CO_3 (104 mg, 2.5 equiv) in dioxane/H_2O (10 mL/2 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 100 °C overnight under N_2 atmosphere. LC-MS showed one main peak with desired MS was detected. The reaction mixture was cooled to rt, extracted with EA, washed with brine, dried over Na_2SO_4 and concentrated. The result residue was purified by silica gel flash chromatography to give compound **8** as a white solid (175 mg, yield = 91%). LC-MS (ESI) m/z: 641.93 [M+1].

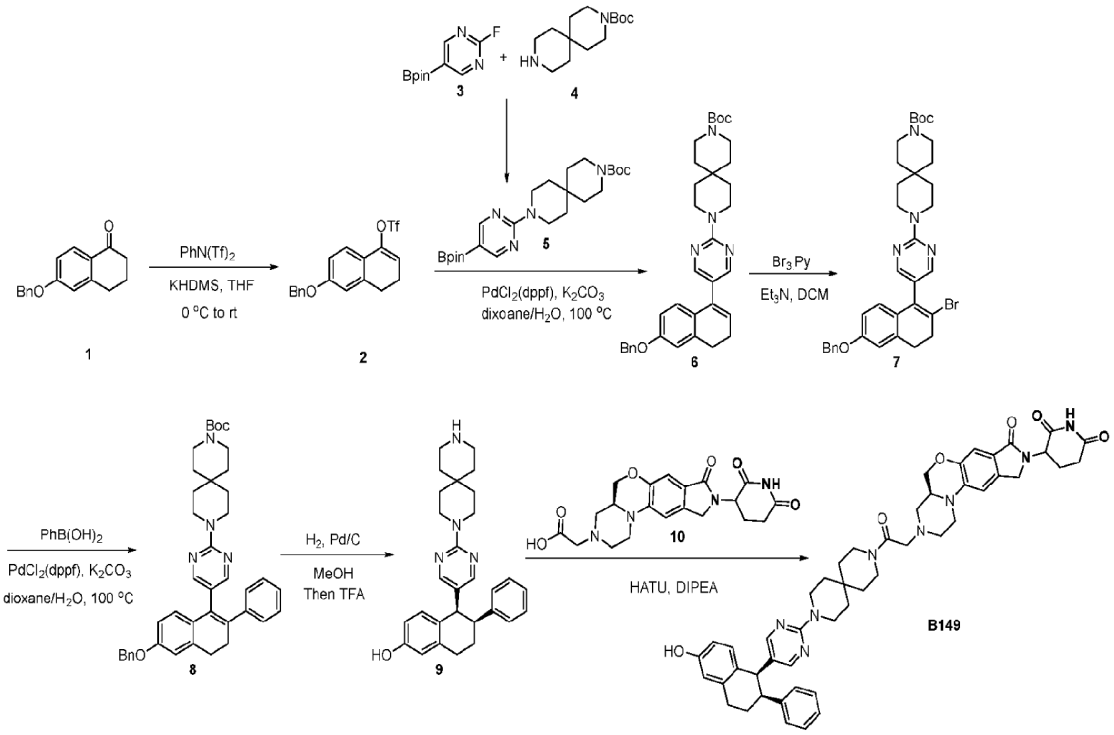
Step 6: (5S,6S)-5-(6-(3,9-diazaspiro[5.5]undecan-3-yl)pyridin-3-yl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

[0805] A mixture of **8** (50 mg, 1.0 equiv) and Pd/C (10% Pd/C powder, 20 mg, 40%) in MeOH was degassed and purged with N_2 3 times, and then the mixture was stirred at rt overnight. The mixture was filtered throught Celite, washed with DCM, and the filtration was concentrated. The result residue was dissolved in DCM (4 mL) and TFA (2 mL) was added. 30 Min later, concentrated under reduced pressure to remove the solvent and the desired product **9** was obtained, which was further lyophilized to give a gray solid. LC-MS (ESI) m/z: 454.09 [M+l].

Step 7: 3-((S)-3-(2-(9-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

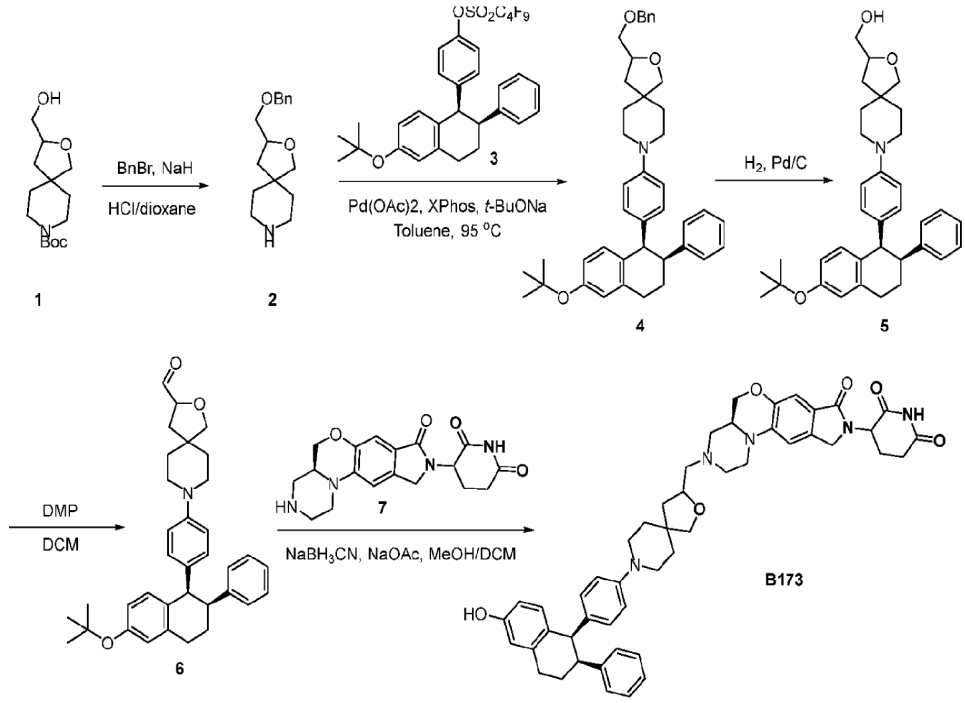
[0806] To a solution of **10** (5.0 mg, 1.0 equiv) in DMF (2.0 mL) was added DIPEA (9.9uL, 6.0 equiv) and HATU (3.6 mg, 1.0 equiv). 10 Min later, compound **9** (6.5 mg, 1.2 equiv) was added and the reaction mixture was stirred for 10-15 min. Then the reaction mixture was inmediately purified by pre-HPLC to obtain the title compound **B148** as a white solid 6.9 mg (yield = 76%). LCMS (ESI) m/z: 850.42 [M+l].

Compound B149: 3-((S)-3-(2-(9-(5-(cis-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0807] Compound **B149** was made using a similar procedure for making compound **B148**. LC-MS (ESI) m/z: 851.38 [M+l].

Compound B173: 3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



Step 1: 3-((benzyloxy)methyl)-2-oxa-8-azaspiro[4.5]decane

[0808] To a solution of **1** (2 g, 1.0 equiv) in DMF was added slowly added NaH (60%, 590 mg, 2.0 equiv) at 0 °C. 30 min Later, BnBr (1.05 mL, 1.2 equiv) was added and the reaction was kept stirring overnight. The next day, quenched with ice-water and extracted with EA. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The result mixture was purified by silica gel flash chromatography to give a colorless oil 2.0 g, which was treated with 4M HCl/dioxane to give compound **2**. LC-MS (ESI) m/z: 262.06 [M+l].

Step 2: 3-((benzyloxy)methyl)-8-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-oxa-8-azaspiro[4.5]decane

[0809] A mixture of **2** (341 mg, 1.5 equiv), **3** (500 mg, 1.0 equiv), $Pd(OAc)_2$ (34.3 mg, 0.2 equiv), XPhos (73 mg, 0.2 equiv) and *t*-BuONa (330 mg, 4.5 equiv) in toluene (18 mL) was degassed with N_2 and then kept stirred at 95 °C overnight. Next, the reaction was cooled to rt, filtered through Celite and the filter cake was washed with DCM. The filtration was concentrated under reduced pressure and the result residue was purified by silica gel flash chromatography to give product **4** (382 mg) as a sticky white silid. LC-MS (ESI) m/z: 616.25 [M+l].

Step 3: (8-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-oxa-8-azaspiro[4.5]decan-3-yl)methanol

[0810] A mixture of **4** (382 mg, 1.0 equiv) and Pd/C (10%, 382 mg) in MeOH/EA was degassed with H_2 and stirred under H_2 atmosphere for 2 days. Then the reaction mixture was filtered and the filtration was concentrated under reduced pressure. The result residue was purified by silica gel flash chromatography to give product **5** as a colorless oil. LC-MS (ESI) m/z: 526.21 [M+l].

Step 4: 8-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-oxa-8-azaspiro[4.5]decane-3-carbaldehyde

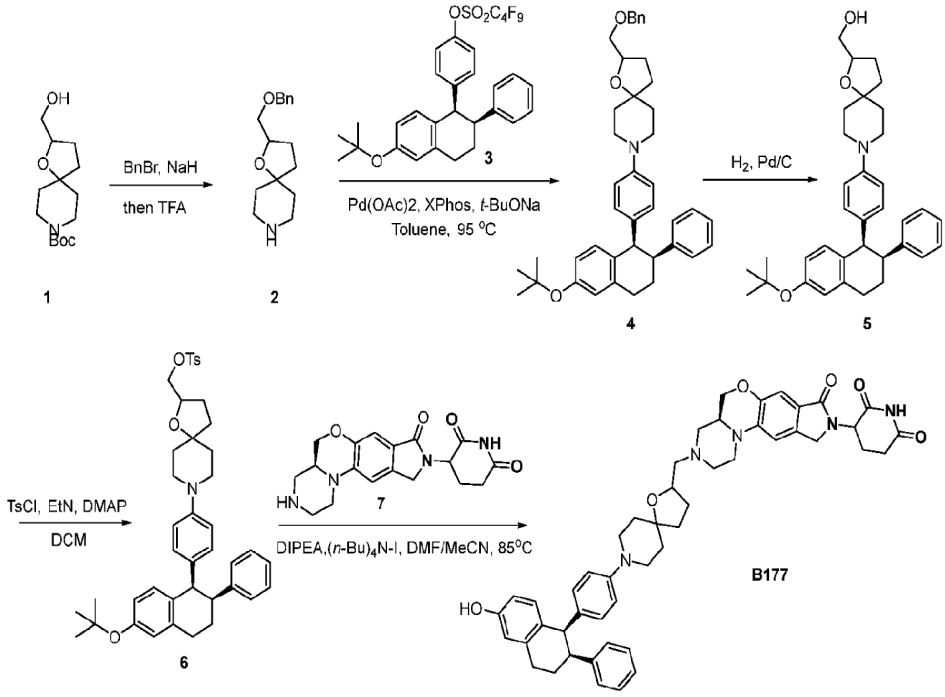
[0811] To a solution of **5** (50 mg, 1.0 equiv) in DCM (8 mL) was added DMP (168.5 mg, 1.7 equiv). The reaction mixture was stirred at rt for 2 h, then diluted with DCM, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The result residue was purified by silica gel flash chromatography to provide compound 6 as a purple solid 44 mg. LC-MS (ESI) 542.29 m/z: [M+H_2O+l].

*Step 5: 3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (**B173**)*

[0812] To a solution of **6** (14 mg, 1.5 equiv) and **7** (6.4 mg, 1.0 equiv) in MeOH/DCM (3 mL/1 mL) was added $NaBH_3CN$ in potions (6.6 mg, 6.0 equiv). 24 h Later, the solvent was removed, and the result residue was purified by pre-HPLC, which was further treated with TFA togive the final compound **B173** as a white solid. LC-MS (ESI) m/z: 808.15 [M+l].

[0813] Compounds **B172**, **B174**, **B175** were prepared using the similar procedure for making **B173**.

Compound B177: 3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



Step 1: 2-((benzyloxy)methyl)-1-oxa-8-azaspiro[4.5]decane

[0814] To a solution of **1** (1 g, 1.0 equiv) in DMF was added slowly added NaH (60%, 295 mg, 2.0 equiv) at 0 °C. 30 min Later, BnBr (526 uL, 1.2 equiv) was added and the reaction was kept stirring overnight. The next day, quenched with ice-water and extracted with EA. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The result mixture was purified by silica gel flash chromatography to give a light-yellow oil 1.08 g, which was treated with 4M HCl/dioxane to give compound **2** as a brown oil 1.1 g. LC-MS (ESI) m/z: 262.06 [M+l].

Step 2: 2-((benzyloxy)methyl)-8-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decane

[0815] A mixture of **2** (341 mg, 1.5 equiv), **3** (500 mg, 1.0 equiv), $Pd(OAc)_2$ (34.3 mg, 0.2 equiv), XPhos (73 mg, 0.2 equiv) and *t*-BuONa (330 mg, 4.5 equiv) in toluene (18 mL) was degassed with N_2 and then kept stirred at 95 °C overnight. Next, the reaction was cooled to rt, filtered through Celite and the filter cake was washed with DCM. The filtration was concentrated under reduced pressure and the result residue was purified by silica gel flash chromatography to give product **4** (387 mg) as a sticky white silid. LC-MS (ESI) m/z: 616.26 [M+l].

Step 3: (8-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-2-yl)methanol

[0816] A mixture of **4** (387 mg, 1.0 equiv) and Pd/C (10%, 387 mg) in MeOH was degassed with H_2 and stirred under H_2 atmosphere for 24 h. Then the reaction mixture was filtered, and the filtration was concentrated under reduced pressure. The result residue was purified by silica gel flash chromatography to give product **5** as a white foam 150 mg. LC-MS (ESI) m/z: 526.19 [M+1].

Step 4: (8-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-2-yl)methyl 4-methylbenzenesulfonate

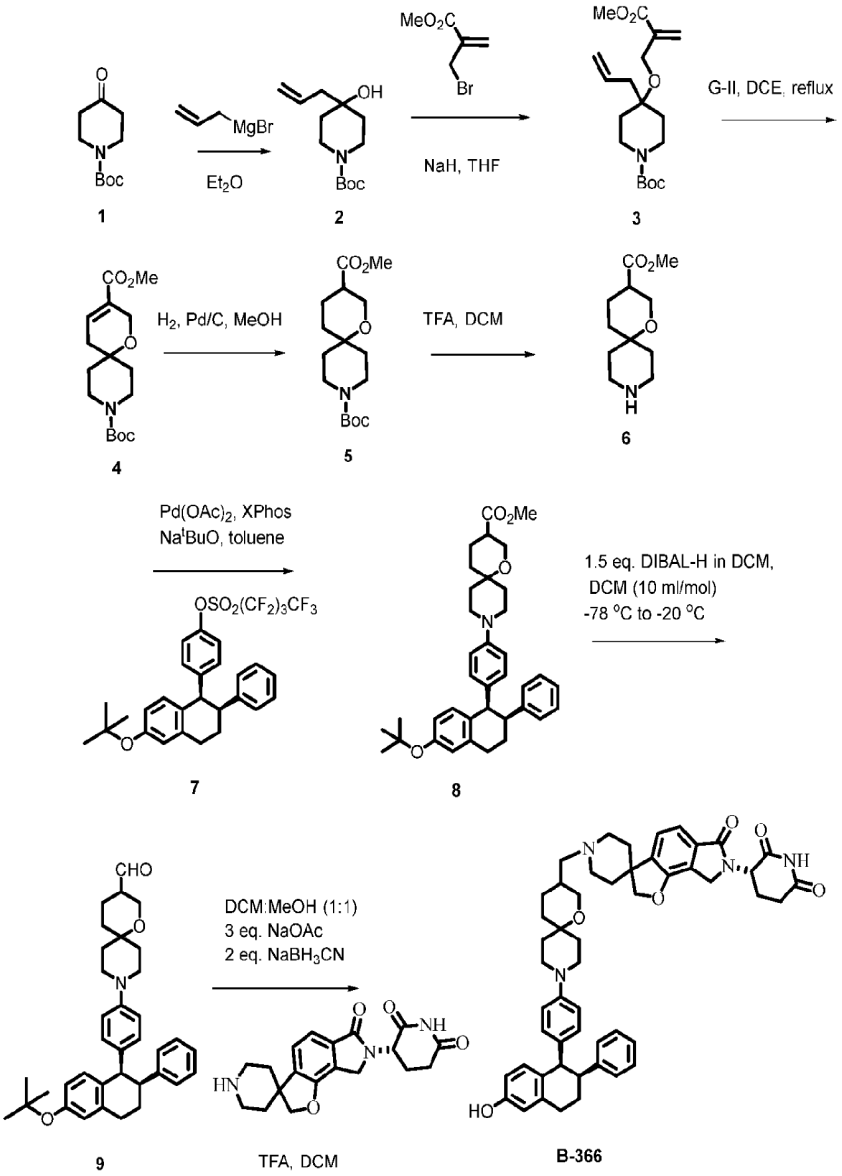
[0817] To a solution of **5** (150 mg, 1.0 equiv), Et_3N (119 uL, 3.0 equiv) and DMAP (6.9 mg, 0.2 equiv) in DCM was added TsCl (81.5 mg, 1.5 equiv). The reaction mixture was stirred at rt overnight, then quenched with water, extracted with EA. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The result residue was prufified by silica gel flash chromatography to give product **6** as a white foam 211 mg. LC-MS (ESI) m/z: 680.25 [M+1].

Step 5: 3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

[0818] To a mixture of **6** (17.4 equiv, 0.8 equiv), **7** (15 mg, 1.0 equiv) and $(n\text{-Bn})_4N\text{-I}$ (29 mg, 2.5 equiv) in DMF/MeCN (2 mL/2 mL) was added DIPEA (111 uL, 20 equiv). The reaction mixture was stirred at 85 °C for 2 days, then purified by pre-HPLC to give the pure intermediate, which was treated with TFA to provide the final compound **B177**. LC-MS (ESI) m/z: 808.10 [M+1].

Compounds **B176** and **B178** were prepared using the similar procedure for making **B177**.

Compound B366. (3S)-3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



Step 1: tert-butyl 4-allyl-4-hydroxypiperidine-1-carboxylate

[0819] Allyl magnesium bromide (1M sol. in Et_2O, 26 mL) was added at 0 °C to a solution of N-Boc-4-piperidone (**1**, 4.03 g, 20 mmol) in Et_2O (80 mL). It was stirred for 10 min. The reaction mixture was warmed to room temperature and stir for 4 h. Followed by quenching by addition of sat. aq. NH_4Cl. It was then extract with EtOAc. The organic phase was separated and washed twice with water then brine, then dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixture was purified using column chromatography on silica gel (0% to 100% ethyl acetate in hexanes. The desired compound **2** (4.84 g, ~ 90% yield) was obtained as a colorless oil.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.77 - 5.94 (m, 1 H), 5.19 (dd, J = 10.4, 1.8 Hz, 1 H), 5.14 (dd, J = 17.1, 1.9 Hz, 1 H), 3.81 (dt, J = 13.4, 3.3 Hz, 2 H), 3.08 -3.24 (m, 2 H), 2.23 (d, J = 7.6 Hz, 2 H), 1.53 (dd, J = 10.4, 4.8 Hz, 4 H), 1.46 (s, 9 H).

Step 2: tert-butyl 4-allyl-4-((2-(methoxycarbonyl)allyl)oxy)piperidine-1-carboxylate

[0820] A 60% oil dispersion of sodium hydride (0.438 g, 1.2 eq) was added to a solution of tert-butyl 4-allyl-4-hydroxypiperidine-1-carboxylate (**2**, 2.2 g, 1 eq) in anhydrous DMF (10 mL/mmol) and the mixture cooled to 0°C. The mixture was warmed to room temperature over 1 hour and methyl 2-(bromomethyl)acrylate (1.63 g, 1 eq) in DMF was added dropwise to the solution over 5 minutes. The mixture was stirred for 12 h. The reaction mixture cooled down to 0°C, a saturated solution of ammonium chloride was added to the reaction mixture and the mixture was diluted with ethyl acetate. The organic phase was separated and washed twice with water then brine, then dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixture was purified using column chromatography on silica gel (0% to 100% ethyl acetate in hexanes, Rf: 0.3; 30% EA/Hx). The desired compound **3** was obtained as a colorless oil. Yield: 60-70%

Step 3: 9-(tert-butyl) 3-methyl 1-oxa-9-azaspiro[5.5]undec-3-ene-3,9-dicarboxylate

[0821] tert-butyl 4-{[2-(methoxycarbonyl)prop-2-en-1-yl]oxy}-4-(prop-2-en-1-yl)piperidine-1-carboxylate (**3**, 340 mg, 1 eq) in anhydrous 1,2-dichloroethane (20 mL/mmol) was combined with G-II (0.05 eq) and the mixture was heated at 50°C for 4 h. The mixture was cooled to room temperature and quenched by passing air. It was then filtered and evaporated and purified by flash. tert-butyl 3-oxo-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (**4**) was obtained as an oil. Yield: ~80%

Step 4: 9-(tert-butyl) 3-methyl 1-oxa-9-azaspiro[5.5]undecane-3,9-dicarboxylate

[0822] Pd/C (100 mg, 10% wt.) was added to a solution of compound **4** (1 gm, 3.31 mmol) in MeOH (33 mL, 10 mL/mmol). The reaction mixture was degassed with H_2 and stirred under a H_2 atmosphere for 12 h at room temperature. The mixture was then filtered through celite and washed with MeOH. Concentration under reduced pressure followed by purification by flash chromatography (0% to 100% ethyl acetate in hexanes) gave the desired compound **5** in 60% yield.

Step 5: methyl 1-oxa-9-azaspiro[5.5]undecane-3-carboxylate

[0823] To a solution of **5** (300 mg) in DCM (5 mL) was added TFA (2.5 mL). The reaction mixture was stirred overnight, then concentrated under reduced pressure and used for the next steps without further purification.

Step 6: methyl 9-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecane-3-carboxylate

[0824] A mixture of 4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (654 mg, 1.0 eq), **6** (319 mg, 1.5 eq), $Pd(OAc)_2$ (73 mg, 0.15 eq), XPhos (73 mg, 0.2 eq) and *t*-BuONa (257 mg, 3.5 eq) in tolune (20 mL) was degassed and purged with N_2 three times, and then the mixture was stirred at 90 °C for 3 h under N_2 atmosphere. LC-MS showed one main peak with desired MS was detected. TLC (PE:EA = 10:1) indicated the starting material was consumed completely, and a new spot formed. The mixture was cooled, diluted with EA, filtered through Celite, the filter cake was washed with EA. The filtrate was concentrated. The residue was purified by silica gel flash chromatography (0% to 50% ethyl acetate in hexanes). The desired product **7** (340 mg, 60% yield) was obtained as a colorless oil. LCMS (ESI) m/z: 568.30 [M+l].

Step 7: 9-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecane-3-carbaldehyde

[0825] To a solution of **7** (567 mg, 1.0 mmol, 10 mL/mmol) in DCM at -78°C, 1.5 mL of DIBAL-H (1.0 M in DCM) was added dropwise. Then, the temperature was slowly increased to -20 °C and stirred for 6 h. After that, the reaction was slowly quenched with satd. Na_2SO_4 at 0 °C and was then filtered and washed several times with EtOAc. Purification by flash chromatography to obtain the desired product (**8**) LCMS (ESI) m/z: 55.20 [M+l8].

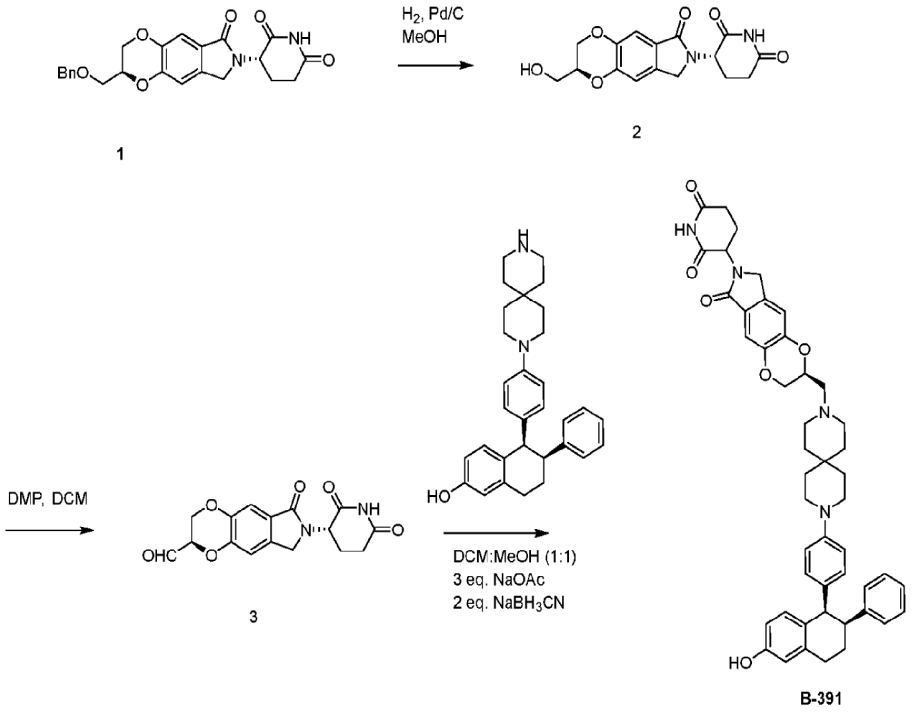
Step 8: (3S)-3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

[0826] To a mixture of compound **8** (53 mg, 0.1 eq.) in methanol (5 mL) and dichloromethane (5 mL) was added (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (35 mg, 0.1 eq.), and AcONa (24 mg, 0.3 eq.). The mixture was stirred at 25 °C for 20 mins, then sodium cyanoborohydride (0.2 mL, 0.2 eq., 1M in THF) was added and

the mixture was further stirred for 10 mins. LCMS showed the reaction was complete. Next, the reaction mixture was concentrated under reduced pressure.

[0827] The crude reaction mixture was dissolved in DCM (10 mL), and then TFA (3 mL) was added. 1 h later, LC-MS showed starting material was consumed completely, and a new peak with desired MS was detected. Next, the reaction mixture was quenched with water and concentrated under reduced pressure. It was purified by pre-HPLC, and the desired product (**B366**) was obtained as white solid. LCMS (ESI) m/z: 821.40 [M+l].

Compound B391: 3-((S)-2-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-6-oxo-2,3,6,8-tetrahydro-7H-[1,4]dioxino[2,3-f]isoindol-7-yl)piperidine-2,6-dione



Step 1: (S)-3-((S)-2-(hydroxymethyl)-6-oxo-2,3,6,8-tetrahydro-7H-[1,4]dioxino[2,3-f]isoindol-7-yl)piperidine-2,6-dione

[0828] Pd/C (42 mg, 10% wt.) was added to a solution of compound **1** (422 mg, 1 mmol) in MeOH (30 mL). The reaction mixture was degassed with H_2 and stirred under a H_2 atmosphere for 2 h at room temperature. The mixture was then filtered through celite, concentration under reduced pressure and used as a crude for the next steps.

Step 2 (R)-7-((S)-2,6-dioxopiperidin-3-yl)-6-oxo-2,3,7,8-tetrahydro-6H-[1,4]dioxino[2,3-f]isoindole-2-carbaldehyde

[0829] To a solution of **2** (1.0 eq., 330 mg) in DCM (10 mL) was added DMP (1.2 eq.) at 0 °C and stirred it for 30 mins. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The reaction mixture was then diluted with DCM, washed with brine, dried over and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **3** in (70% yield). LC/MS (ESI) m/z: 348.12 ($M+H_2O$).

Step 3 3-((S)-2-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)-6-oxo-2,3,6,8-tetrahydro-7H-[1,4]dioxino[2,3-f]isoindol-7-yl)piperidine-2,6-dione

[0830] To a mixture of compound **3** (33 mg, 0.1 eq.) in methanol (4 mL) and dichloromethane (4 mL) was added (5R,6S)-5-(4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)-6-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol (45 mg, 0.1 eq.), and AcONa (24 mg, 0.3 eq.). The mixture was stirred at 25 °C for 20 mins, then sodium cyanoborohydride (0.2 mL, 0.2 eq., 1M in THF) was added and the mixture was further stirred for 10 mins. LCMS showed the reaction was complete. Next, the reaction mixture was concentrated under reduced pressure. It was purified by pre-HPLC, and the desired product (**B-391**) was obtained as white solid. LCMS (ESI) m/z: 767.28 [M+l].

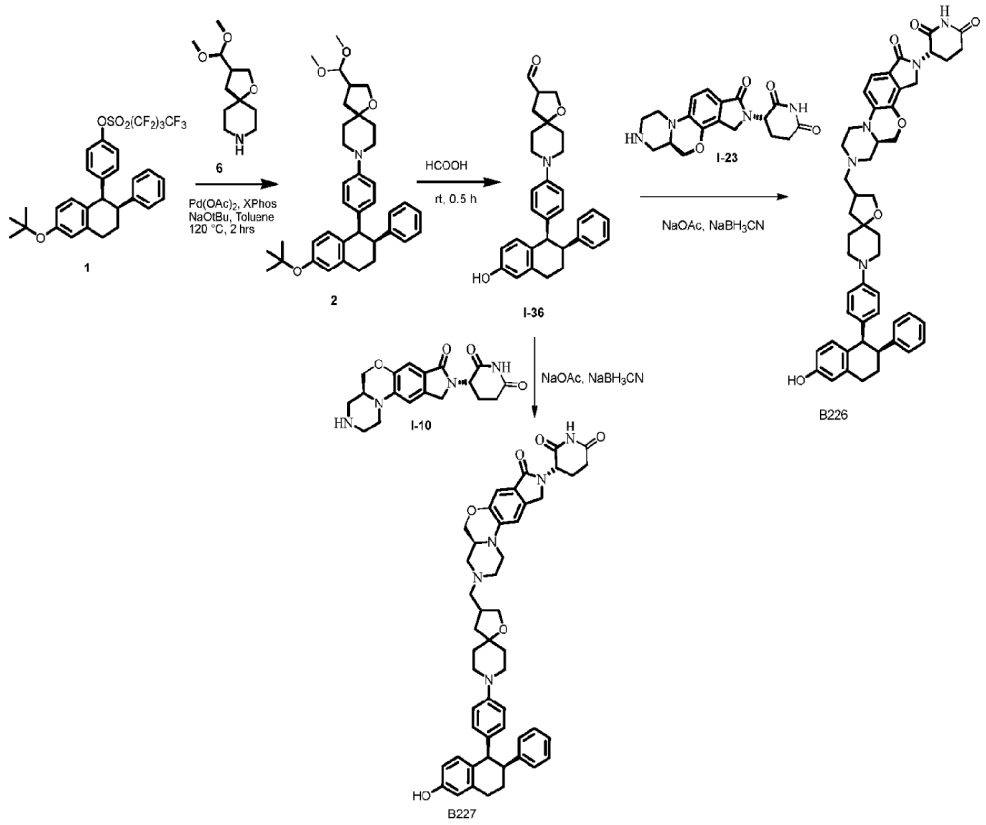
[0831] The following compounds were prepared using the similar procedure for making **B391**:

Table 6. Compounds Prepared According to Compounds B391

Compound No.	$(M+H)^+$
B387	767.19
B388	739.19
B392	767.19
B393	739.19

Compound B226. ***(3S)-3-((5aR)-7-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione***

Compound B227. (3S)-3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione.



Step 1: 8-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane:

[0832] To a mixture of 4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl) phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (100 mg, 0.15 mmol, 1.0 eq), 3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (39 mg, 0.18 mmol, 1.0 eq), t-BuONa (44 mg, 0.46 mmol, 3.0cq) and Xphos (7 mg, 0.02 mmol, 0.1 cq) in toluene (5 mL) was added $Pd(OAc)_2$ (13 mg, 0.02 mmol, 0.1 eq), then stirred at 120 °C for 2 hours. LC-MS showed the reaction was completed. The reaction mixture was cooled to rt, the mixture was diluted with water and washed with EtOAc, the organic phase was dried with Na_2SO_4 and concentrated under vacuum. the residue was purified by SiO_2 column chromatography (EtOAc:PE=1:20) to afford *8-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-*

azaspiro[4.5]decane (66 mg, 77%) as a yellow oil. LC-MS purity: 62.1% (UV at 254 nm), LC-MS: 570.3 $[M+H]^+$.

Step 2: 8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde

[0833] To a mixture of 7-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (66 mg, 0.11 mmol, 1 eq) in HCOOH (3 mL) was stirred at 25 °C for 0.5 hour. The mixture was concentrated to give crude product 7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (48 mg, 90%) as a colorless liquid. LC-MS purity: 100 % (UV at 254 nm), LC-MS: 468.2 $[M+H]^+$.

Step 36-3&4: (3S)-3-((5aR)-7-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

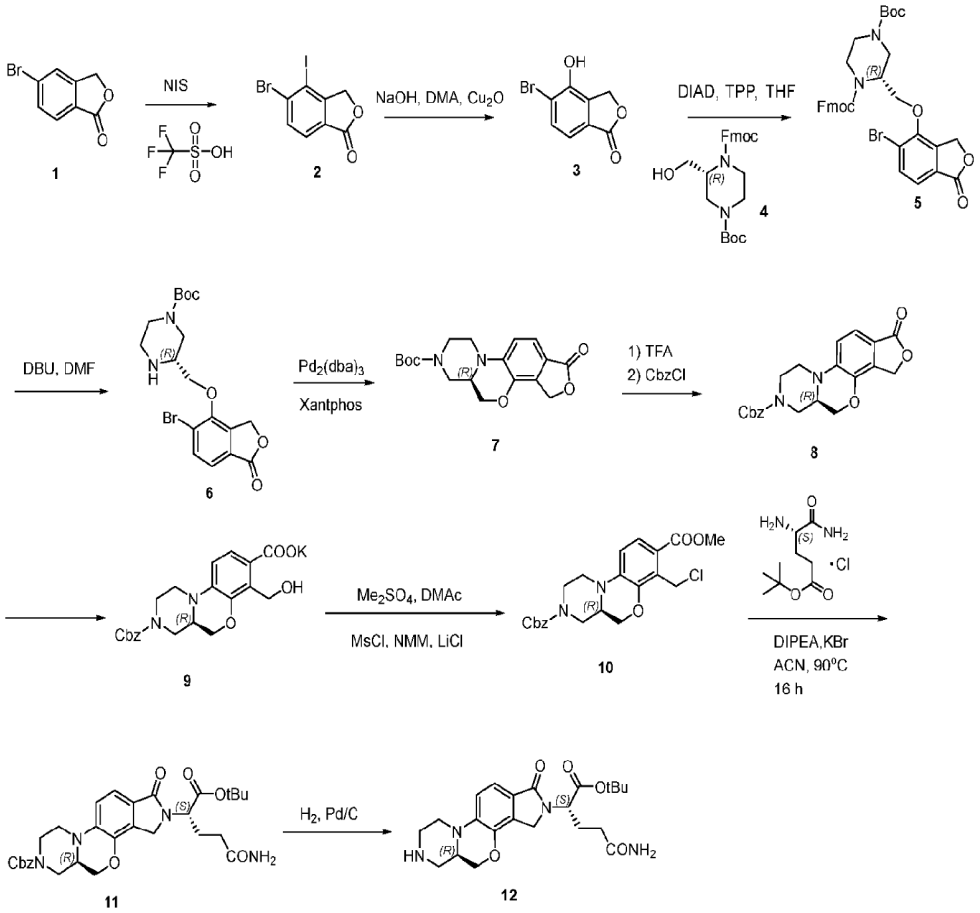
[0834] To a solution of I-23 (1.2 equiv) in Methanol:DCM (4:1) was added NaOAc (2 equiv) and the mixture was stirred at room temperature for 5 mins. The aldehyde **I-36** (1 equiv) in MeOH: DCM (4:1) was then added to the reaction mixture and stirred for another 10 mins. Sodiumcyanoborohydride (2 equiv) and Acetic acis was then added to the reaction sequentialy and stirred for another 15 minutes. UPLC chromatography showed the completion of the reaction, and the product was purified using preparative HPLC. LC/MS (ESI) m/z: 808.4 (M+H).

[0835] (3S)-3-((4aS)-3-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione: LC/MS (ESI) m/z: 808.4 (M+H).

Compound 226X. ***(S)-3-((R)-7-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione***

Compound 226Y. ***(S)-3-((R)-7-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-***

1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



Step 1:

[0836] To a solution of 5-Bromo-3H-isobenzofuran-1-one (**1**) (50 g, 1 eq.) in trifluoromethanesulfonic acid (400 mL, 20 eq.) was added NIS (62.5 g, 1.2 eq.) at 0 °C in portions. The mixture was allowed to warm to room temperature and stirred overnight. TLC showed no starting material remained and two new spots formed. The reaction mixture was poured into ice-water and yellow solid precipitated. The mixture was filtered and the filter cake was washed with ice cold water. The filter cake was dissolved in DCM and washed with 1 (M) $Na_2S_2O_3$ followed by dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated to afford a yellow solid. The crude product was purified by silica gel flash chromatography. The less polar product (top spot on TLC) **2** was obtained as a brown solid (40 g, yield = 50%), and the more polar product **2b** (bottom spot on TLC) was obtained as a brown solid which was not further reacted in next step.

Step 2:

[0837] To a mixture of compound **2** (20 g, 1 eq.), sodium hydroxide (11.5 g, 5 eq.) in water (200 mL, 1.5 M) and N,N-dimethylacetamide (100 mL) was added cuprous oxide (1.7 g, 0.2 eq.). The reaction mixture was heated to 80 °C and stirred for 12 h. TLC showed the reaction was completed. The reaction mixture neutralized using 1 (N) hydrochloride solution and extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate. The crude product was purified by silica gel column chromatography to give compound **3** was obtained as a white solid (6.88 g, 51% yield).

Step 3:

[0838] To a solution of compound **3** (7 g, 1 eq.) in 120 ml of THF/DCM (V/V = 2:1), compound **4** (20 g, 1.5 eq.) and PPh_3 (12 g, 1.55 eq.) was added. The reaction mixture was cooled to 0° C and DIAD (9.5 mL, 1.55 eq.) was added dropwise. The resultant mixture was then stirred overnight at room temperature. The solvent was evaporated at reduced pressure and the crude product was purified by silica gel column chromatography using 0-100% EtOAc/hexane. The desired product **5** was obtained as a yellow foam (7 g, yield = 35%).

Step 4:

[0839] To a solution of compound **5** (5 g, 1 eq.) in DMF (0.2 M) was added DBU (2 g). After TLC showed the reaction was completed, the mixture was diluted with ethyl acetate and washed with water. The combined organic phases were washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo to give an oil. The crude product was purified by silica gel column chromatography using 0-5% DCM in methanol to give compound **6** (2.8 g yield 85%). LC/MS (ESI) m/z: 426.08 $[M+H]^+$.

Step 5:

[0840] A vial was charged with compound **6** (2.8 g, 0.38 mmol, 1 eq.), $Pd_2(dba)_3$ (0.15 eq.), XantPhos (0.3 eq.), Cs_2CO_3 (5 eq.) and dioxane (100 mL). The mixture was purged with nitrogen and heated to 100 °C for 6 h. TLC showed reaction was complete. The mixture was diluted with ethyl acetate and washed with water. The organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by silica gel column chromatography using 0-50% EtOAc/hexane to give compound **7** as a yellow foam (1.25 g, yield 55%), LC/MS (ESI) m/z: 347.15 $[M+H]^+$.

Step 6:

[0841] To a stirred solution of compound **7** (2.55 g, 7.4 mmol, 1 eq.) in DCM (10 mL) at room temperature was added TFA (10 mL) slowly and the reaction mixture was stirred at rt for 1 hour. Once the reaction was completed, the mixture was concentrated and the residue was used directly for next step. The residue was diluted with DCM (50 mL), added TEA (2.3 g, 22.1 mmol, 3 eq.) and cooled to 0 °C was added CbzCl (1.8 g, 11.1 mol, 1.5 eq.) and the mixture was warmed to 25 °C and stirred for 3 h. Then, water and DCM were added and the organic phase was separated, washed with brine, dried and concentrated. The residue was further purified by silica column chromatography eluting with 30% EtOAc in PE to give compound **8** (2.5 g, 89%) as a light yellow solid.

Step 7:

[0842] A slurry of the compound **8** (3.1 g, 8.16 mmol) in i-PrOH (50 mL) and water (0.5 mL) was stirred in a reactor at ambient temperature. Potassium hydroxide (502 mg, 8.97 mmol) was charged as a solid. The resulting slurry was heated to T = 35-40 °C and held at that temperature for 2 h. The slurry was cooled to 20-25 °C, and then was filtered. The cake was washed with a mixture of i-PrOH and water. The cake (**9**) was dried at 25 °C under vacuum which was used directly for next step.

Step 8:

[0843] The compound **9** (3.56 g, 8.16 mmol) was slurried in DMAc (50 mL) at 10 °C in a three necks flask. Me_2SO_4 (1.08 g, 8.57 mmol, 1.05 equiv.) was added dropwise at 10 °C. The resulting mixture was stirred at this temperature for 3 h. NMM (2.47 g, 24.5 mmol) was then added to the mixture, followed by the slow addition of MsCl (1.86 g, 16.3 mmol), maintaining 10-15 °C. The resulting mixture was stirred at this temperature for 30 minutes. LiCl (514 mg, 12.2 mmol) was added as a solid in a single portion. The resulting slurry was heated to 35-40 °C for 1-2 h. The slurry was cooled to 20-25 °C and quenched with H_2O (200 mL). The mixture extracted with EtOAc (5 × 50 mL) and the organic layer dried over Na_2SO_4, filtered, and evaporated to afford the crude product, which was purified by flash silica chromatography to afford the compound **10** (2.1 g, two steps, 60%).

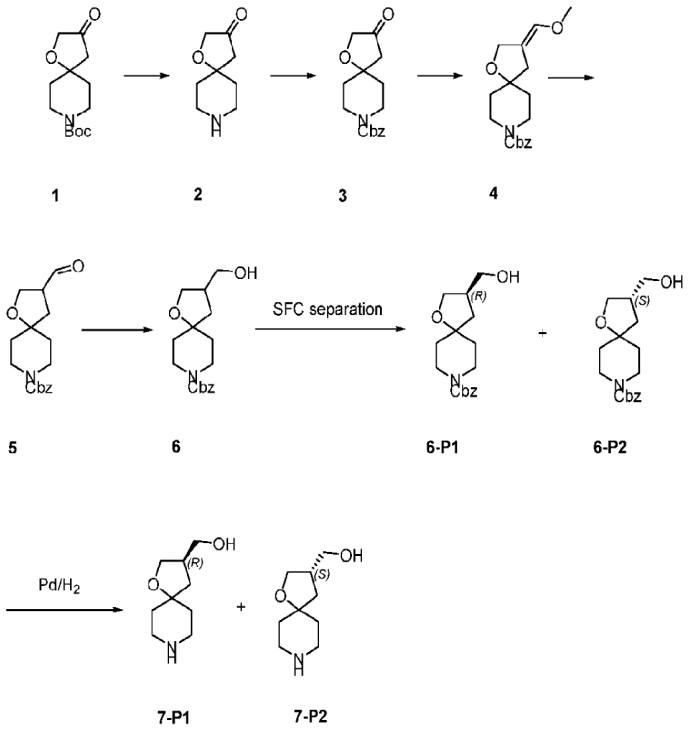
Step 9:

[0844] To a 100 mL reactor was charged **10** (900 mg, 2.09 mmol), tert-Butyl (S)-4,5-diamino-5-oxopentanoate hydrochloride (748 mg, 3.13 mmol), and potassium bromide (372 mg, 3.13 mmol), followed by acetonitrile (20 mL), and diisopropylethylamine (808 mg, 6.26 mmol). The resulting

mixture was stirred at 90 °C for 16 h. The reaction was then cooled to 20 °C and diluted with water. The aqueous layer was extracted with EtOAc (3 ×50 mL). The combined organic phase was washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to afford crude product. The crude product was purified by flash silica chromatography to yield **11** (500 mg) LC-MS: $[M+H]^+$: 565.

Step 10:

[0845] A 2,2,2-Trifluoroethanol solution of the product **11** (500 mg) from Step 9 was added palladium on activated carbon catalyst (0.15 eq., 10% purity) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen three times.The mixture was heated at 25°C for 3h, then filtered and concentrated in vacuo. The residue was used directly for next step. LC-MS: $[M+H]^+$: 431.



Step 1-2:

[0846] To a stirred solution of compound **1** (5 g, 0.0196 mol, 1 eq.) in EtOAc (50 mL) at room temperature was added conc. HCl (10 g, 0.098 mol, 5 eq.) slowly and the reaction mixture was stirred at rt for 1 hour. Once the reaction was completed, the mixture was diluted with EtOAc (50 mL), poured into Na_2CO_3 suspension (20.8 g, 0.196 mol, 10 eq., in 100 mL of water) and the

mixture was stirred for 20 min. To the mixture was added CbzOSu (4.9 g, 0.0196 mmol, 1 eq.) and the mixture was stirred for 1 h. The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by silica column chromatography eluting with 50% EtOAc in PE to give compound **3** (5.6 g, 100%) as a light yellow oil.

Step 3:

[0847] To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (16.6 g, 0.071 mol, 2.5 eq.) in dried THF (100 mL) cooled at -70 °C was added NaHMDS (19.4 mL, 0.0470 mol, 2 eq.) dropwise and the mixture was warmed to 0 °C slowly and stirred for 2 h. Then the mixture was cooled at -70 °C and a solution of compound **3** (5.6 g, 0.1 mol, 1 eq.) in THF (50 mL) was added. The mixture was warmed to rt slowly and stirred for 2 h. TLC was done to detect the process of the reaction. Once no starting material was left, the mixture was quenched by NH_4Cl solution (150 mL) and diluted with EtOAc (200 mL). The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by silica column chromatography eluting with 30% EtOAc in PE to give compound **4** (5.8 g, 94%) as a light yellow oil.

Step 4:

[0848] A solution of compound **4** (5.8 g, 0.0183 mol, 1 eq.) in ACN (80 mL) and 2M HCl (40 mL) was stirred at rt for 4 hours. TLC were done to detect the process of the reaction. Once the reaction was completed, the mixture was quenched by water (100 mL) and extracted with EtOAc (100 mL*3). The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by silica column chromatography eluting with 30% EtOAc in PE to give compound **5** (4.6 g, 0.0153 mol, 78%) as a light yellow oil.

Step 5:

[0849] To a stirred solution of compound **5** (4.6 g, 0.0153 mol, 1.0 eq) in MeOH (100 mL) cooled at 0 °C was added $NaBH_4$ (0.88 g, 0.0231 mol, 1.5 eq.) and the mixture was warmed to 0~25 °C and stirred for 1 h. TLCs were done to detect the process of the reaction. Once the reaction was completed, the mixture was quenched by water (100 mL) and extracted with EtOAc (100 mL*3). The organic phase was separated, dried, concentrated and the residue was purified by silica column chromatography eluting with 50% EtOAc in PE to give compound **6** (4.5 g, 0.015 mol, 98%) as a light yellow oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.27 (m, 5H), 5.12 (s, 2H), 3.95 (dd, *J* = 9.0, 7.2 Hz, 1H), 3.76 – 3.55 (m, 5H), 3.36 (m, 2H), 2.61 – 2.48 (m, 1H), 1.90 (dd, *J* = 12.7, 8.6 Hz, 1H), 1.81– 1.45 (m, 4H), 1.42 (dd, *J* = 12.7, 7.6 Hz, 1H).

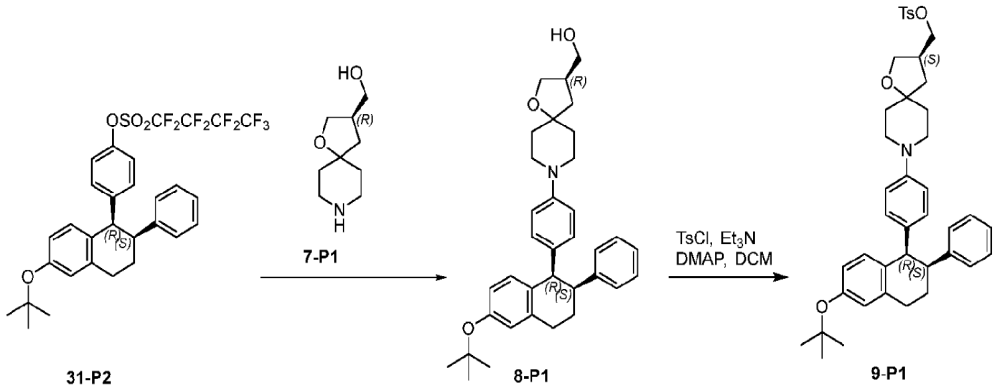
Step 6:

[0850] The compound **6** was further separated by preparative SFC (Column: ChiralPak AD, 250×30mm I.D., 10μm, Mobile phase: A for CO2 and B for Ethanol, Gradient: B 40%, Flow rate: 140 mL /min, Back pressure: 100 bar) to afford a pure product **6-P1** (2 g) and a pure product **6-P2** (2 g).

Step 7:

[0851] To a solution of compound **6-P1** (0.78 g, 1 eq.) in CF_3CH_2OH (15 mL) was added Pd/C (0.3 g, 10% on Carbon, wetted with ca. 55% water) and the mixture was stirred at rt for 12 hours under H_2 (balloon). TLC were done to detect the process of the reaction. Once the reaction was completed, the catalyst was removed by filtration and the filtrate was concentrated to give compound **7-P1** (0.43 g, 100%) .

[0852] According to the same procedure, the title compound **7-P2** was provided as a colorless oil.



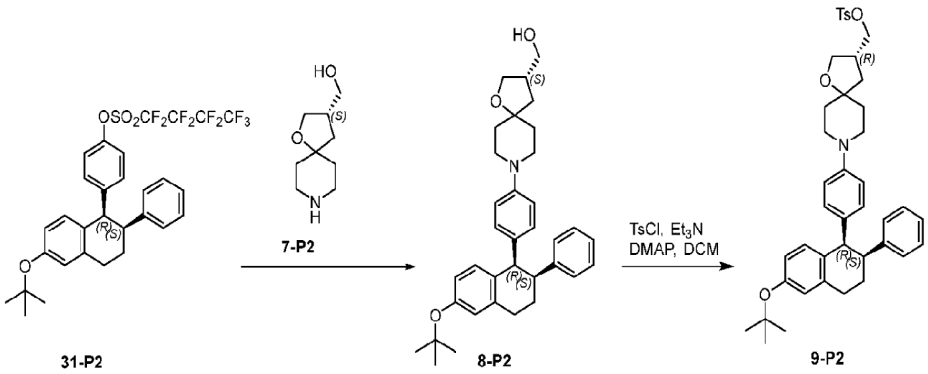
STEP 1:

[0853] A round bottomed flask equipped with a stirrer bar was charged with a mixture of compound **31-P2** (650 mg, 1 mmol), chiral amine **7-P1** (205 mg, 1.2 mmol), cesium carbonate (650 mg, 2 mmol), and t-BuXphoxPd-G(III) (*CAS: 1447963-75-8*, 80 mg, 0.1 mmol). The flask was evacuated and back-filled with nitrogen (x 3). *t*-Amyl alcohol (10 mL) was added and the mixture stirred at 100 °C for 10 hours. The cooled reaction mixture was diluted with EtOAc and filtered through Celite™ to remove insoluble material. The filtrate was washed with water, saturated aqueous sodium chloride and then dried over magnesium sulfate, filtered and the filtrate concentrated. The crude material was purified by flash silica chromatography, elution gradient MeOH in DCM. Pure fractions were combined and concentrated to afford compound **8-P1** (180 mg, 35%). LC-MS: $[M+H]^+$: 526; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.19 – 7.10 (m, 3H), 6.88

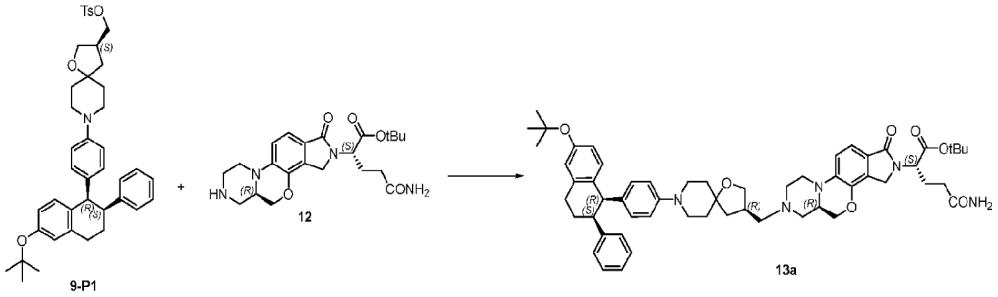
– 6.77 (m, 4H), 6.72 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 2H), 6.25 (d, *J* = 8.4 Hz, 2H), 4.22 (d, *J* = 5.0 Hz, 1H), 3.97 (dd, *J* = 9.0, 7.2 Hz, 1H), 3.65 (m, 5H), 3.36 (m, 1H), 3.10 (m, 5H), 2.55 (m, 1H), 2.24 – 2.11 (m, 2H), 1.93 (m, 1H), 1.76-1.62 (m, 5H), 1.36 (s, 9H).

STEP 2:

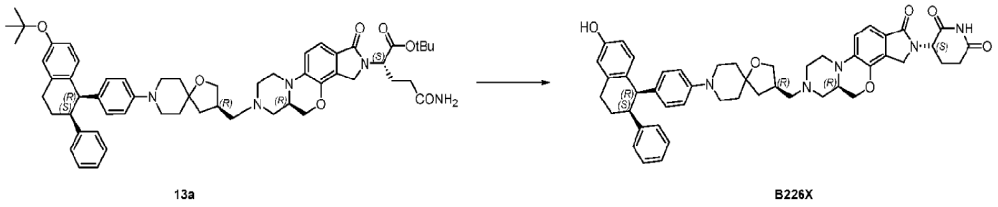
[0854] To a solution of compound **8-P1** (180 mg, 0.34 mmol, 1 eq.) in DCM (5 mL) was added TEA (0.68 mmol, 2 eq.) and DMAP (0.04 mmol, 0.2 eq.). The flask was evacuated and back-filled with nitrogen. TsCl (0.51 mmol, 1.5 eq.) was added and the mixture stirred at R.T. overnight. TLC indicated the starting material was consumed completely. The reaction mixture was quenched by addition of saturated NH_4Cl solution, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by flash silica chromatography to give compound **9-P1** (150 mg, 65%). LC-MS [M+H] $^+$: 680; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.14 (m, 3H), 6.88 – 6.82 (m, 2H), 6.81 – 6.77 (m, 2H), 6.72 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 2H), 6.26 (d, *J* = 8.3 Hz, 2H), 4.22 (d, *J* = 5.0 Hz, 1H), 4.04 – 3.93 (m, 2H), 3.89 (m, 1H), 3.54 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.36 (ddd, *J* = 13.2, 5.4, 2.2 Hz, 1H), 3.05 (m, 6H), 2.71 – 2.60 (m, 1H), 2.45 (s, 3H), 2.17 (m, 1H), 1.89 (dd, *J* = 12.9, 8.7 Hz, 1H), 1.79 (m, 1H), 1.74 – 1.66 (m, 3H), 1.60 (m, 2H), 1.36 (s, 9H).



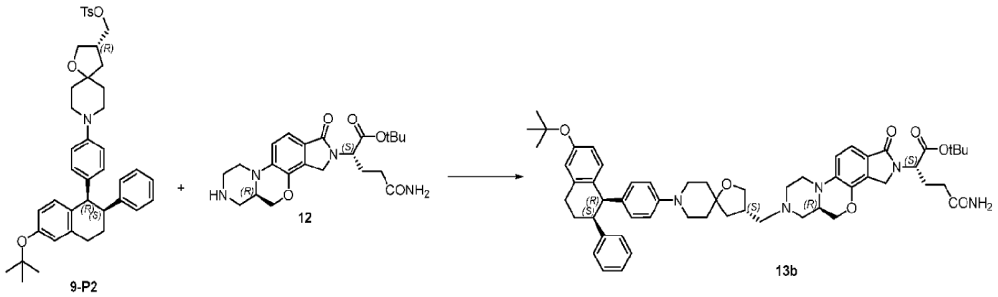
[0855] According to the same procedure, chiral amine **7-P2** was applied to afford compound **9-P2**, LC-MS: [M+H] $^+$: 680; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.14 (m, 3H), 6.88 – 6.82 (m, 2H), 6.80 (dd, *J* = 7.3, 2.2 Hz, 2H), 6.72 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.54 (d, *J* = 8.6 Hz, 2H), 6.24 (d, *J* = 8.6 Hz, 2H), 4.22 (d, *J* = 4.9 Hz, 1H), 4.02 – 3.82 (m, 3H), 3.54 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.41 – 3.29 (m, 1H), 3.05 (m, 6H), 2.66 (m, 1H), 2.45 (s, 3H), 2.16 (m, 1H), 1.89 (m, 1H), 1.78 (m, 1H), 1.36 (s, 9H).



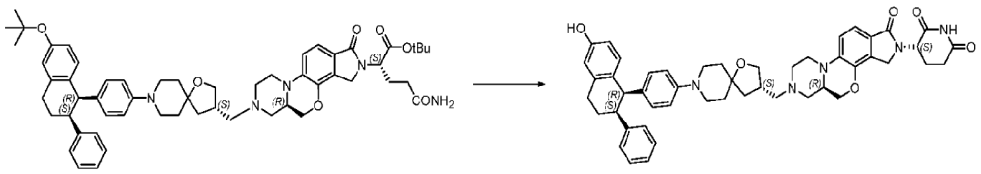
[0856] To a solution of compound **9-P1** (160 mg, 0.235 mmol, 1 eq.) in acetonitrile (2 mL) was added **12** (111 mg, 0.258 mmol, 1.1 eq.), KI (40 mg, 0.235 mmol, 1.0 eq.) and diisopropylethylamine (0.12 mL, 3 eq.). The mixture was stirred at 90 °C for 24 hours. LC-MS showed the reaction was completed. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers was washed wash brine, dried with anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuum. The residue was purified was purified by flash silica chromatography (DCM:MeOH = 10:1) to give the title compound **13a** (160 mg, 72%), LC-MS: $[M+H]^+$: 938.5.



[0857] To a solution of compound **13a** (100 mg, 0.11 mmol, 1 eq.) in acetonitrile (3 mL) was added benzenesulfonic acid (70 mg, 0.44 mmol, 4 eq.). The mixture was stirred at 80 °C for 3 hours. LC-MS showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by preparative reverse phase HPLC (ACN:H_2O = 25-55% (1‰ TFA) to provide the title compound **B226X** (53 mg, 60 %). LC-MS: $[M+H]^+$: 808.4.



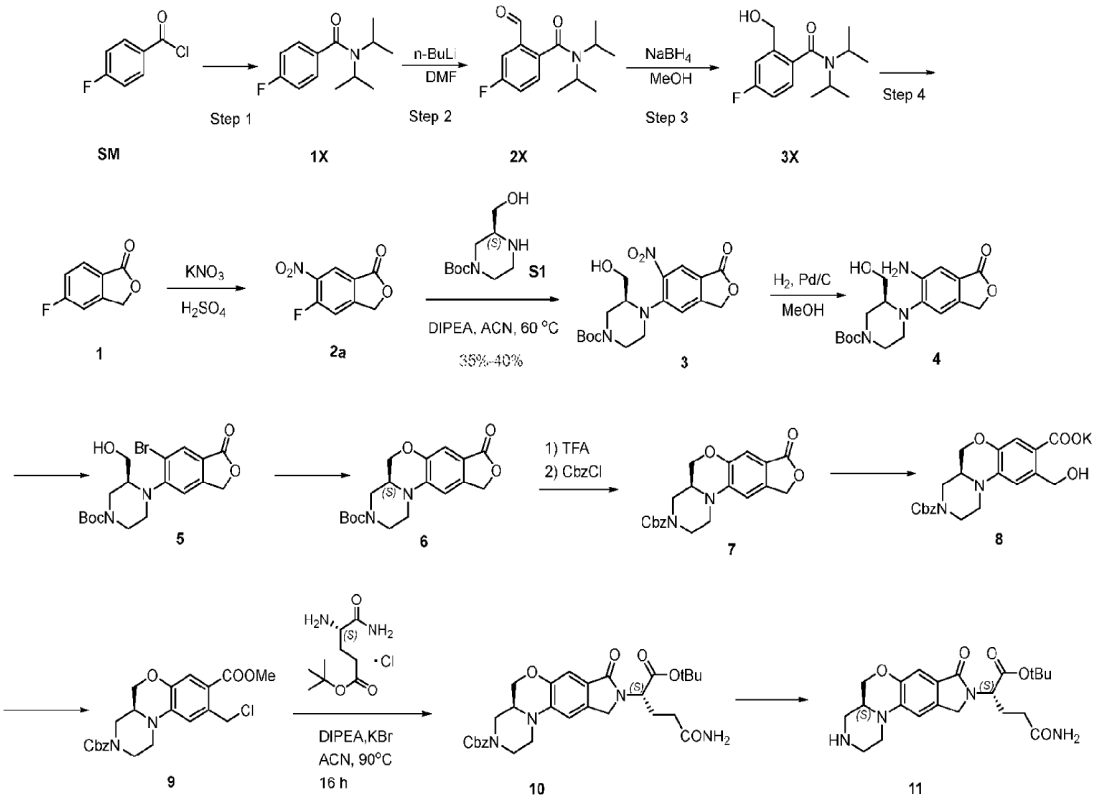
[0858] To a solution of compound **9-P2** (160 mg, 0.235 mmol, 1 eq.) in acetonitrile (2 mL) was added **12** (111 mg, 0.258 mmol, 1.1 eq.), KI (40 mg, 0.235 mmol, 1.0 eq.) and diisopropylethylamine (0.12 mL, 3 eq.). The mixture was stirred at 90 °C for 24 hours. LC-MS showed the reaction was completed. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed wash brine, dried with anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuum. The residue was purified was purified by flash silica chromatography (DCM:MeOH = 10:1) to give the title compound **13b** as a white solid. LC-MS: $[M+H]^+$: 938.5.



[0859] To a solution of compound **13b** (100 mg, 0.11 mmol, 1 eq.) in acetonitrile (3 mL) was added benzenesulfonic acid (70 mg, 0.44 mmol, 4 eq.). The mixture was stirred at 80 °C for 3 hours. LC-MS showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by preparative reverse phase HPLC (ACN:H_2O = 25-55% (1‰ TFA) to provide the title compound **B226Y** as a white solid. LC-MS: $[M+H]^+$: 808.4.

Compound 227X. ***(S)-3-((S)-3-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione***

Compound 227Y. ***(S)-3-((S)-3-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione***



Step 1:

[0860] A mixture of diisopropylamine (382.9 g, 3.78 mol, 1.2 eq.) and K_2CO_3 (522.9 g, 3.78 mol, 1.2 eq.) in toluene (1500 mL) and water (1500 mL) was added to a solution of **SM** (500 g, 3.15mol, 1.0 eq.) at 5-15°C. After stirring for 3 h at ambient temperature, the aqueous layer was extracted with ethyl acetate. Then, the organic layer was further washed with 1N HCl. and brine, dried over $MgSO_4$, and evaporated. The residue was triturated with hexane (200 mL), and the crystalline product was collected by filtration to give **1X** (500 g, 71%) as colorless crystals.

Step 2:

[0861] n-Butyllithium (948 mL of a 2.5 M solution in hexane, 2.37 mol, 1.1 eq.) was added to a solution of **1X** (500 g, 2.24 mol, 1.0 eq.) in dry THF (3000 mL) at - 78 ° C. After stirring for 1 h at -78 ° C, DMF (173 g, 2.37mol, 1.1 eq.) was added, while the temperature of the mixture rose to -70 ° C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (2000 mL) and extracted with ethyl acetate (2000 mL). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuum to give **2X** as a white solid (483 g, 85% yield).

Step 3:

[0862] Sodium borohydride (72.8 g, 1.0 eq.) was added in portion to a solution of **2X** (483 g, 1.0 eq.) in dry methanol (3000 mL) and cooled with ice - water bath. After stirring for 10 h, the solvent was evaporated, water (1000 mL) was added to the residue, and the mixture was extracted with diethyl ether (2000 mL). The ethereal layer was washed with brine, dried over $MgSO_4$. The solvent was removed in vacuum to give **3X** as a beige solid (450 g, 93% yield).

Step 4:

[0863] A mixture of **3X** (450 g) and aqueous hydrochloric acid (6 M, 2250 mL) was refluxed for 10 h. After cooling to ambient temperature it was extracted with ethyl acetate (3 × 1500 mL). The combined organic layer was extracted with sat. $NaHCO_3$ (1500 Ml) and then washed with brine, dried over $MgSO_4$, and evaporated. The residue was triturated with a mixture (20:1) of PE and ethyl acetate (300 mL) and collected by filtration to give **1** (52%)

Step 5:

[0864] To a solution of **1** (30 g, 1.0 equiv) in H_2SO_4 (150 mL) was added KNO_3 (1.5 equiv, 30 g) in potionwise. The reaction mixture was stirred at rt for 3 h. TLC (PE:EA = 2:1) indicated the starting material was consumed completely and two new spot formed. The reaction mixture was slowly poured into ice water, then extracted with EA, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue which was purified by silica gel flash chromatography. The minor product **2b** (the less polar product) was obtained as a white solid (8 g, yield = 20%), and the major product **2a** (the more polar product) was obtained as a white solid (30 g, yield = 80%).

Step 6:

[0865] To a solution of **2a** (1.0 equiv, 10 g) and **S1** (1.2 equiv, 13.2 g) in acetonitrile (100 mL) was added DIPEA (2.5 equiv, 22 mL), and the reaction mixture was stirred at 60 °C for 6 h. TLC (DCM:MeOH = 20:1) showed the starting material **2a** was completely consumed. Then the reaction mixture was concentrated under reduced pressure and the result residue was purified by silica gel flash chromatography. The desired product **3** was obtained as a yellow foam (7 g, yield = 35%).

Step 7:

[0866] To a solution of **3** (10 g, 1.0 equiv) in MeOH (100 mL) was added Pd/C (2 g, 20% w). The reaction mixture was degassed and purged with H_2 three times and keep stirred at rt overnight. UPLC-MS showed the starting material completely conversed to desired product **4**. Then the

reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure to give a residue which was purified by silica gel flash chromatography. The desired product **4** was obtained as a yellow solid (8.3 g, yield = 90%).

Step 8:

[0867] To a stirred solution of **4** (5 g, 1 eq.) in dry acetonitrile (100.0 mL) was added $CuBr_2$ (2.76 g, 0.9 eq) at 0 °C. After 5 min, a solution of *tert*-butyl nitrite (1.9 mL, 1.2 eq) in dry acetonitrile (5.0 mL) was added and the reaction mixture was stirred for 0.5 h. TLC (DCM: MeOH = 50:1, R_f = 0.5). The mixture was diluted with ethyl acetate, washed with saturated sodium bisulfite, dried (Na_2SO_4), filtered and concentrated in vacuo. Purify the residue by silica gel column chromatography and elute with MeOH/DCM (0% to 2%). The desired product **5** was obtained as a yellow solid (3.2 g, yield = 55%).

Step 9:

[0868] A vial was charged with **5** (3.6 g, 1 eq.), $Pd(OAc)_2$ (0.42 g, 0.2 eq.), JohnPhos (3.2 g, 1.2 eq.), Cs_2CO_3 (9 g, 3 eq.) and toluene (200 mL). The mixture was purged with nitrogen and heated to 90 °C for 6 h. TLC (ethyl acetate: petroleum ether = 1:1) showed reaction was complete. The mixture was filtered and the filtrate was concentrated in vacuum. The crude product was triturated with Et_2O to afford the title compound **6** as a beige solid (1.75 g, 60% yield).

Step 10:

[0869] To a stirred solution of compound **6** (2.55 g, 7.4 mmol, 1 eq.) in DCM (10 mL) at room temperature was added TFA (10 mL) slowly and the reaction mixture was stirred at rt for 1 hour. Once the reaction was completed, the mixture was concentrated and the residue was used directly for next step. The residue was diluted with DCM (50 mL), added TEA (2.3 g, 22.1 mmol, 3 eq.) and cooled to 0 °C was added CbzCl (1.8 g, 11.1 mol, 1.5 eq.) and the mixture was warmed to 25 °C and stirred for 3 h. Then, water and DCM were added and the organic phase was separated, washed with brine, dried and concentrated. The residue was further purified by silica column chromatography eluting with 30% EtOAc in PE to give compound **7** (2.24 g, 80%) as a light yellow solid.

Step 11:

[0870] A slurry of the compound **7** (5 g, 8.16 mmol) in i-PrOH (50 mL) and water (0.5 mL) was stirred in a reactor at ambient temperature. Potassium hydroxide (502 mg, 8.97 mmol) was charged as a solid. The resulting slurry was heated to T = 35-40 °C and held at that temperature for 2 h.

The slurry was cooled to 20-25 °C, and then was filtered. The cake was washed with a mixture of i-PrOH and water. The cake (**8**) was dried at 25 °C under vacuum which was used directly for next step.

Step 12:

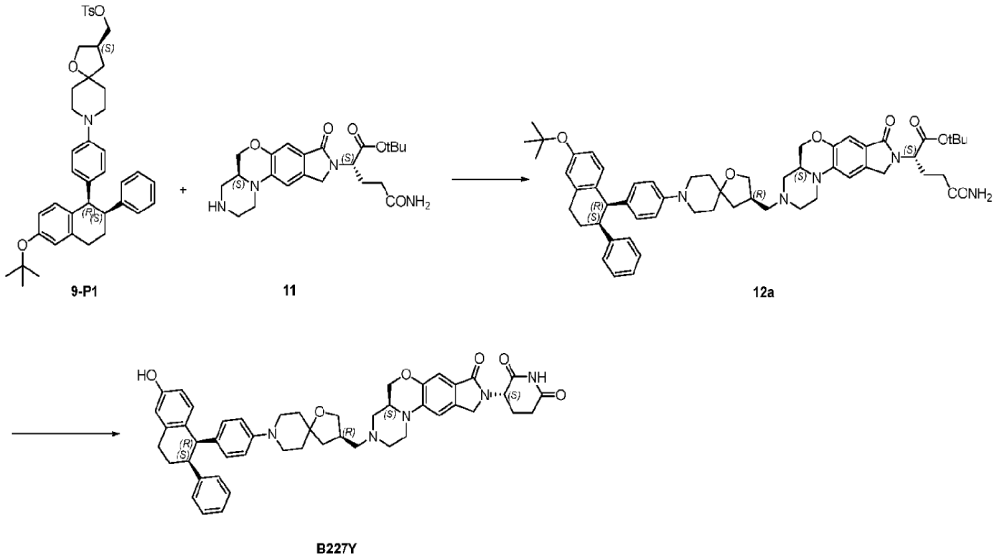
[0871] The compound **8** (3.56 g, 8.16 mmol) was slurried in DMAc (50 mL) at 10 °C in a three necks flask. Me_2SO_4 (1.08 g, 8.57 mmol, 1.05 equiv.) was added dropwise at 10 °C. The resulting mixture was stirred at this temperature for 3 h. N-methylmorpholine (NMM) (2.47 g, 24.5 mmol) was then added to the mixture, followed by the slow addition of MsCl (1.86 g, 16.3 mmol), maintaining 10-15 °C. The resulting mixture was stirred at this temperature for 30 minutes. LiCl (514 mg, 12.2 mmol) was added as a solid in a single portion. The resulting slurry was heated to 35-40 °C for 1-2 h. The slurry was cooled to 20-25 °C and quenched with H_2O (200 mL). The mixture extracted with EtOAc (5 × 50 mL) and the organic layer dried over Na_2SO_4, filtered, and evaporated to afford the crude product, which was purified by flash silica chromatography to afford the compound **9** (2.1 g, two steps, 60%)

Step 13:

[0872] To a 100 mL reactor was charged **9** (900 mg, 2.09 mmol), tert-Butyl (S)-4,5-diamino-5-oxopentanoate hydrochloride (748 mg, 3.13 mmol), and potassium bromide (372 mg, 3.13 mmol), followed by acetonitrile (20 mL), and diisopropylethylamine (808 mg, 6.26 mmol). The resulting mixture was stirred at 90 °C for 16 h. The reaction was then cooled to 20 °C and diluted with water. The aqueous layer was extracted with EtOAc (3 ×50 mL). The combined organic phase was washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to afford crude product. The crude product was purified by flash silica chromatography to yield **10** (500 mg) LC-MS: $[M+H]^+$: 565.4.

Steps 14:

[0873] A 2,2,2-Trifluoroethanol solution of the product **10** (500 mg) from Step 13 was added 10% palladium on activated carbon catalyst (0.15 eq.) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen three times. The mixture was heated at 25°C for 3h, then filtered and concentrated in vacuo. The residue (**11**) was used directly for next step. LC-MS: $[M+H]^+$: 431.2

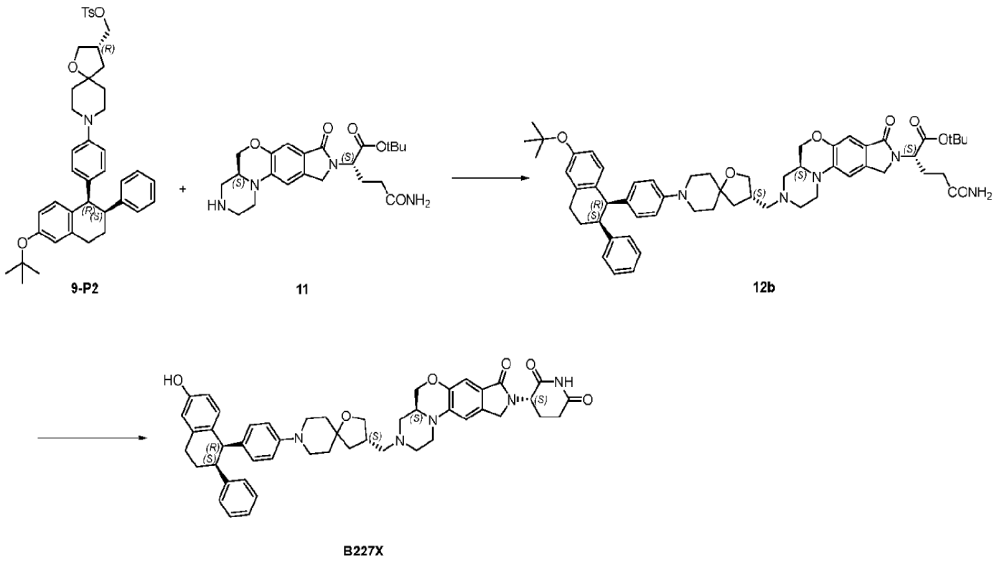


Step 1:

[0874] To a solution of compound **9-P1** (160 mg, 0.235 mmol, 1 eq.) in acetonitrile (2 mL) was added **11** (111 mg, 0.258 mmol, 1.1 eq.), KI (40 mg, 0.235 mmol, 1.0 eq.) and diisopropylethylamine (0.12 mL, 3 eq.). The mixture was stirred at 90 °C for 24 hours. LC-MS showed the reaction was completed. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers was washed wash brine, dried with anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuum. The residue was purified was purified by flash silica chromatography (DCM:MeOH = 10:1) to give the title compound **12a** (155 mg, 70%), LC-MS: $[M+H]^+$: 938.5.

Step 2:

[0875] To a solution of compound **12a** (100 mg, 0.11 mmol, 1 eq.) in acetonitrile (3 mL) was added benzenesulfonic acid (70 mg, 0.44 mmol, 4 eq.). The mixture was stirred at 80 °C for 3 hours. LC-MS showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by preparative reverse phase HPLC (ACN:H_2O = 25-55% (1‰ TFA) to provide the title compound **B227Y** (53 mg, 60 %). LC-MS: $[M+H]^+$: 808.4.



Step 1:

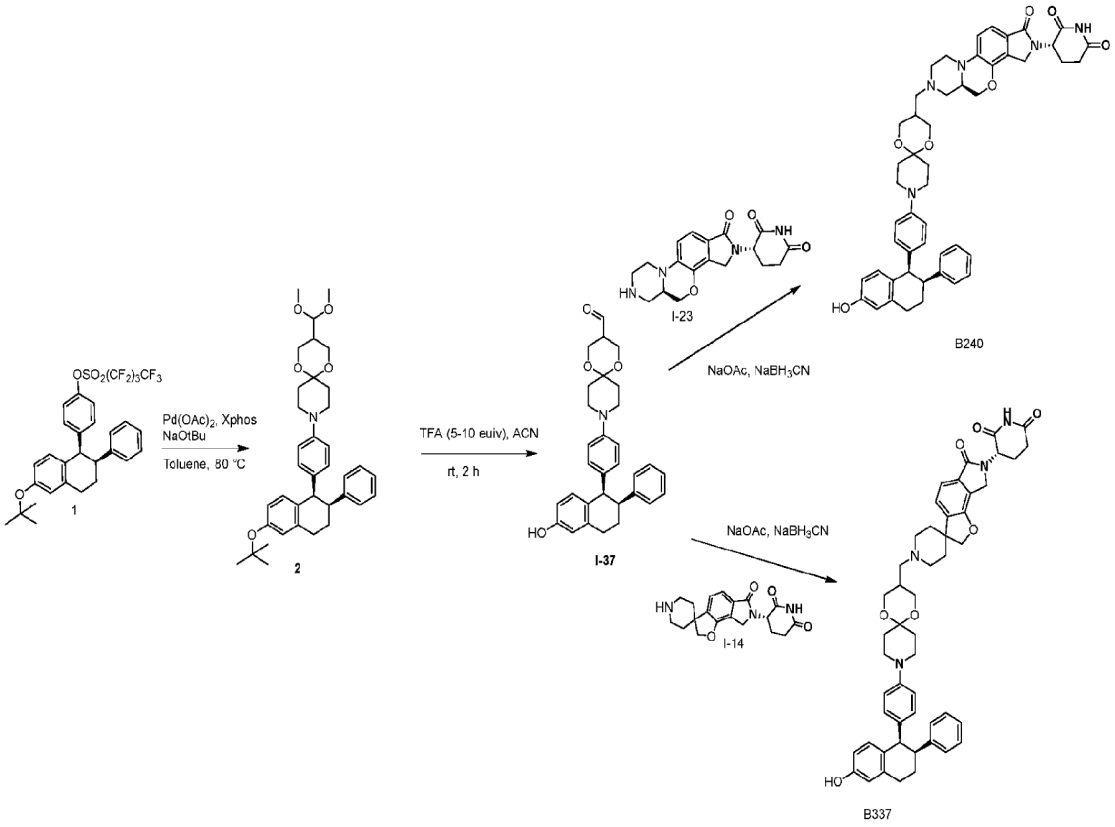
[0876] To a solution of compound **9-P2** (160 mg, 0.235 mmol, 1 eq.) in acetonitrile (2 mL) was added **11** (111 mg, 0.258 mmol, 1.1 eq.), KI (40 mg, 0.235 mmol, 1.0 eq.) and diisopropylethylamine (0.12 mL, 3 eq.). The mixture was stirred at 90 °C for 24 hours. LC-MS showed the reaction was completed. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers was washed wash brine, dried with anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuum. The residue was purified was purified by flash silica chromatography (DCM:MeOH = 10:1) to give the title compound **12b**. LC-MS: $[M+H]^+$: 938.5.

Step 2:

[0877] To a solution of compound **12b** (100 mg, 0.11 mmol, 1 eq.) in acetonitrile (3 mL) was added benzenesulfonic acid (70 mg, 0.44 mmol, 4 eq.). The mixture was stirred at 80 °C for 3 hours. LC-MS showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by preparative reverse phase HPLC (ACN:H_2O = 25-55% (1‰ TFA) to provide the title compound **B227X**. LC-MS: $[M+H]^+$: 808.4.

Compound B240. ***(S)-3-((R)-7-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione***

Compound B337. (S)-3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione.



Step 1: 9-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-3-(dimethoxymethyl)-1,5-dioxa-9-azaspiro[5.5]undecane:

[0878] To a mixture of 4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl) phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (100 mg, 0.15 mmol, 1.0 eq), 3-(dimethoxymethyl)-1,5-dioxa-9-azaspiro[5.5]undecane (42 mg, 0.18 mmol, 1.2 eq), t-BuONa (44 mg, 0.46 mmol, 3.0eq) and Xphos (7 mg, 0.02 mmol, 0.1 eq) in toluene (5 mL) was added $Pd(OAc)_2$ (13 mg, 0.02 mmol, 0.1 eq), then stirred at 120 °C for 2 hours. LC-MS showed the reaction was completed. The reaction mixture was cooled to rt, the mixture was diluted with water and washed with EtOAc, the organic phase was dried with Na_2SO_4 and concentrated under vacuum. the residue was purified by SiO_2 column chromatography (EtOAc:PE=1:20) to afford compound **2** (71 mg, 80%) as a yellow oil. LC-MS purity: 62.1% (UV at 254 nm), LC-MS: 586.3 $[M+H]^+$.

Step 2: 8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde

[0879] To a mixture of 7-(4-((1R,2S)-6-(tert-butoxy)-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (71 mg, 0.119 mmol, 1 eq) in HCOOH (3 mL) was stirred at 25 °C for 0.5 hour. The mixture was concentrated to give crude product 7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (49 mg, 85%) as a colorless liquid. LC-MS purity: 100 % (UV at 254 nm), LC-MS: 484.3 $[M+H]^+$.

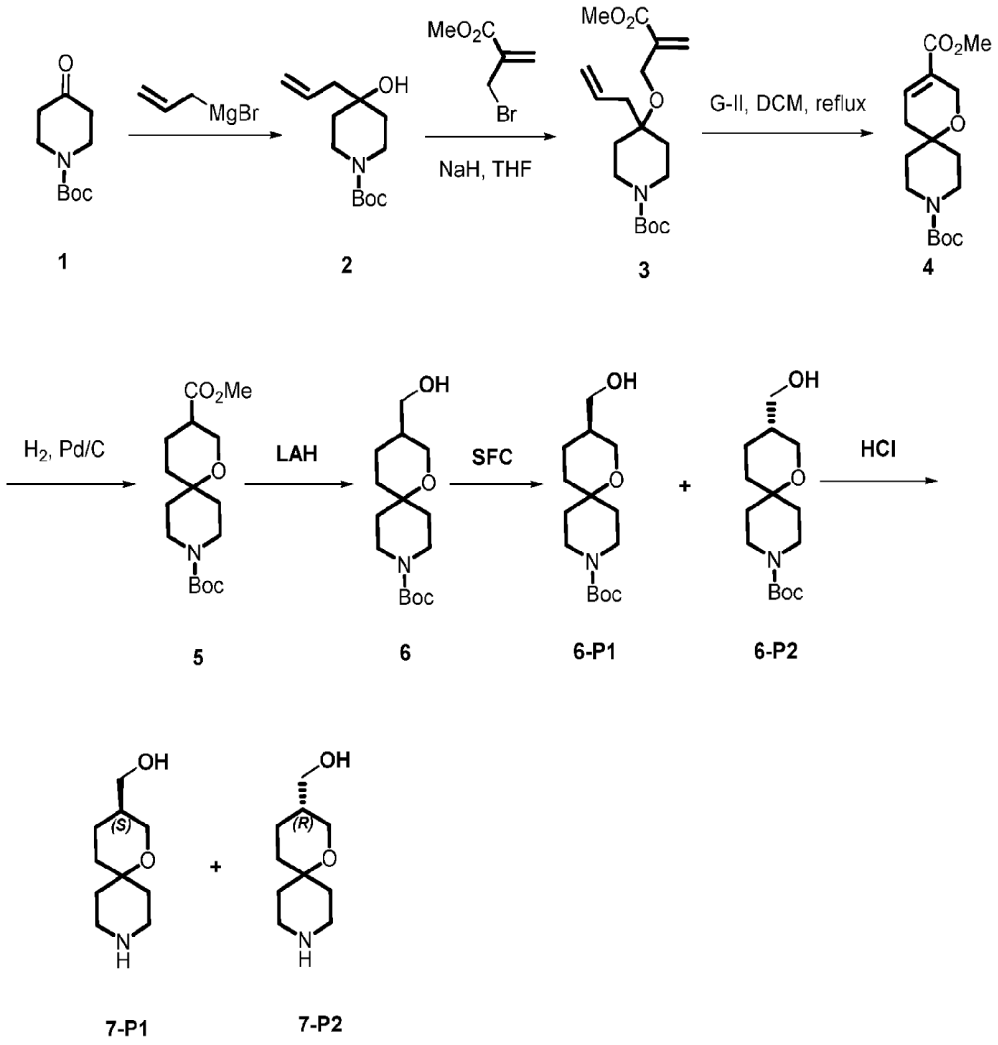
Step 3&4: (S)-3-((R)-7-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

[0880] To a solution of I-23 (1.2 equiv) in Methanol:DCM (4:1) was added NaOAc (2 equiv) and the mixture was stirred at room temperature for 5 mins. The aldehyde **I-37** (1 equiv) in MeOH: DCM (4:1) was then added to the reaction mixture and stirred for another 10 mins. Sodiumcyanoborohydride (2 equiv) and Acetic acis was then added to the reaction sequentialy and stirred for another 15 minutes. UPLC chromatography showed the completion of the reaction, and the product was purified using preparative HPLC. LC/MS (ESI) m/z: 824.4 (M+H).

[0881] (S)-3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione: LC/MS (ESI) m/z: 823.4 (M+H).

Compound B366X. ***(S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione***

Compound B366Y. ***(S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione***



Step 1:

[0882] Add allylmagnesium bromide (15.2 g, 2.5 eq) to a solution of *N*-Boc-4-piperidone (**1**, 10.0 g, 50 mmol) in THF (40 mL). Then added sat. aq. NH_4Cl (40 mL), after that the Zn powder (6.6 g, 2.0 eq.) were added at r.t by three batch, then warm to 40°C and stirred for 16 h. The mixture was diluted in water (200 mL) and extracted by EtOAc (100 mL*3). The organic layers was washed with water and brine, dried (Na_2SO_4) and concentrated. Purify the crude by flash chromatography (20-30% EtOAc/CyHex) to obtain the compound **2** (10.5 g). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.94 - 5.77 (m, 1 H), 5.19 (dd, J = 10.4, 1.8 Hz, 1 H), 5.14 (dd, J = 17.1, 1.9 Hz, 1 H), 3.81 (dt, J = 13.4, 3.3 Hz, 2 H), 3.24 -3.08 (m, 2 H), 2.23 (d, J = 7.6 Hz, 2 H), 1.53 (dd, J = 10.4, 4.8 Hz, 4 H), 1.46 (s, 9 H).

Step 2:

[0883] A 60% oil dispersion of sodium hydride (2.9 g, 2.0 equiv) was added to a solution of tert-butyl 4-allyl-4-hydroxypiperidine-1-carboxylate (**2**, 8.8 g, 1 equiv) in anhydrous DMF (100 mL) and the mixture cooled to 0°C. The mixture was warmed to room temperature over 1 hour and methyl 2-(bromomethyl)acrylate (9.8 g, 1.5 equiv) was added dropwise to the solution over 5 minutes. The mixture was aged for 18 hours. A saturated solution of ammonium chloride was added to the reaction mixture and the mixture was diluted with ethyl acetate. The organic phase was separated and washed twice with water then brine, then dried over sodium sulfate, filtered and concentrated in vacuo. The crude mixture was purified using column chromatography on silica gel (0% to 100% ethyl acetate in hexanes). Yield: 4.3 g of tert-butyl 4-{[2-(methoxycarbonyl)prop-2-en-1-yl]oxy}-4-(prop-2-en-1-yl)piperidine-1-carboxylate as a colorless oil (**3**). LC-MS, $[M+Na]^+$: 362.

Step 3:

[0884] tert-butyl 4-{[2-(methoxycarbonyl)prop-2-en-1-yl]oxy}-4-(prop-2-en-1-yl)piperidine-1-carboxylate from Step 2 (**3**, 2.4 g, 1 equiv) in anhydrous 1,2-dichloroethane (75 mL) was combined with benzylidene [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(tricyclohexylphosphine)ruthenium (0.61 g, 10 mol%) and the mixture was heated at 85°C for overnight. The mixture was cooled to room temperature, then diluted with ethyl acetate and washed with water twice with brine. The separated organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to offer compound **4** as an oil (1.97 g). LC-MS, $[M+Na]^+$ m/z 334. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.99 (dt, *J* = 4.3, 2.3 Hz, 1H), 4.30 (m, 2H), 3.76 (m, 2H), 3.74 (s, 3H), 3.15 (m, 2H), 2.14 (dt, *J* = 4.3, 2.9 Hz, 2H), 1.74 (m, 2H), 1.60 (m, 2H), 1.46 (s, 9H).

Step 4:

[0885] A MeOH solution of the compound **4** from Step 3 was added palladium on activated carbon catalyst (0.15 eq., 10% purity) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen three times. The mixture was heated at 40°C for overnight, then filtered and concentrated in vacuo. The crude mixture was purified using column chromatography on silica gel. The product **5** was provided as an oil. $[M+Na]^+$ m/z 336.

Step 5:

[0886] To a stirred solution of compound **5** (5.8 g, 0.0185 mol, 1.0 eq) in dry THF (100 mL) cooled at 0 °C was added LAH (1.05 g, 0.0278 mol, 1.5 eq.) and the mixture was warmed to 0~25 °C and stirred for 3 h. TLCs were done to detect the process of the reaction. Once the reaction was

completed, the mixture was quenched by water (100 mL) and extracted with EtOAc (100 mL*3). The organic phase was separated, dried, concentrated and the residue was purified by silica column chromatography eluting with 50% EtOAc in PE to give compound **6** (3.58 g, 0.015 mol, 68%) as a light yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.83 – 3.74 (m, 1H), 3.75 – 3.58 (m, 2H), 3.55 – 3.47 (m, 2H), 3.39 (dd, *J* = 11.8, 9.4 Hz, 1H), 3.09 (m, 2H), 2.06 (m, 2H), 1.82 –1.52 (m, 5H), 1.43 (s, 9H), 1.33 –1.22 (m, 2H).

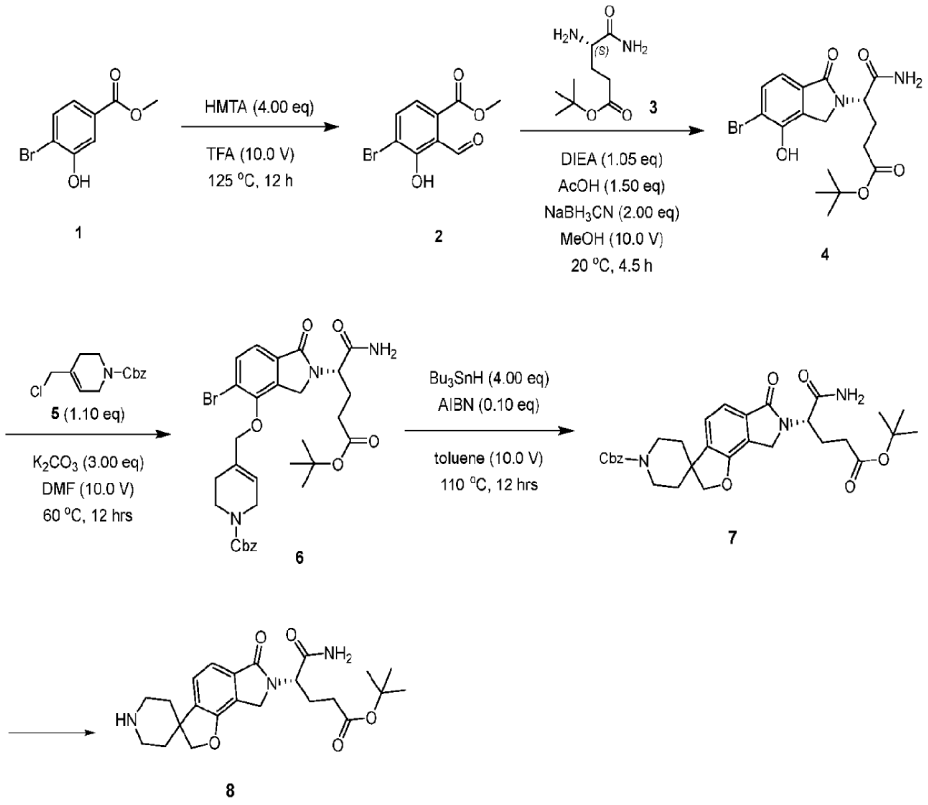
Step 6:

[0887] The compound **6** was further separated by SFC (Instrument: WATERS 150 preparative SFC(SFC-26); Column: ChiralPak AD, 250×30mm I.D., 10m; Mobile phase: A for CO2 and B for Methanol; Gradient: B 20%; Flow rate: 150mL /min; Back pressure: 100 bar) to afford a pure product **6-P1** (2 g) and a pure product **6-P2** (2 g).

Step 7:

[0888] To a solution of compound **6-P1** (2 g, 7 mmol, 1 eq.) in dioxane (10 mL) was added 4M HCl-dioxane (10 mL, 42 mmol, 6 eq.) and the mixture was stirred at rt for 2 h. TLC were done to detect the process of the reaction. The solvent was concentrated to give compound **7-P1** as the HCl salt. LC-MS: [M+H] $^+$: 186.4.

[0889] According to the same procedure, the title compound **7-P2** was provided as HCl salt. LC-MS: [M+H] $^+$: 186.4.



Step 1:

[0890] To a solution of compound **1** (20 g, 86.5 mmol, 1 eq) in TFA (200 mL) was added HMTA (48.5 g, 0.346 mol, 4 eq) at 20 °C. The mixture was stirred at 125 °C for 12 hrs. TLC (Petroleum ether/Ethyl acetate = 5/1) indicated compound **1** was consumed completely and there was desired product. The mixture was quenched with 2N HCl (5 V) and a yellow solid formed. The mixture was stirred for 10 min and then additional water (5 V) was added and stirred for 1 hr. The mixture was filtered. The filter cake was dissolved in DCM and filtered on celite, dried and then remove most of the solvent in vacuo. Compound **2** (14 g, 55 mmol, 61% yield) was obtained as a gray solid, which was indicated by LCMS: $[M-H]^-$: 257.6.

Step 2:

[0891] Add tert-butyl (*S*)-4,5-diamino-5-oxopentanoate **3** (17.3 g, 72.4 mmol, 1.05 eq, HCl) in MeOH (300 mL) at 20 °C; Add DIPEA (9.37 g, 72.4 mmol, 12.6 mL, 1.05 eq) to the mixture; The compound **2** (17.8 g, 69.0 mmol, 1 eq) was added into the mixture at the same temperature, followed by adding AcOH (6.22 g, 103 mmol, 5.92 mL, 1.5 eq). After 1.5 hrs, $NaBH_3CN$ (8.67 g, 138 mmol, 2 eq) was added to the mixture in portions and the mixture was stirred at 20 °C for 3 hrs. TLC (Petroleum ether/Ethyl acetate = 0/1, R_f = 0.8) indicated compound **2** was consumed

completely and LCMS indicated there was desired product. The reaction mixture was quenched by addition H_2O (200 mL) at 20 °C, and then concentrated under reduced pressure to remove MeOH. Then the mixture was extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (200 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Petroleum ether/Ethyl acetate=1/1 to Ethyl acetate).The title compound **4** (20 g, 72% yield) was obtained as a yellow solid, which was detected LCMS: $[M+H]^+$: 413.2.

Step 3:

[0892] Compound **4** (5 g, 12.1 mmol, 1 eq) was added in DMF (50 mL) at 20 °C; The K_2CO_3 (5.02 g, 36.3 mmol, 3 eq) and compound **5** (2.94 g, 12.7 mmol, 1.05 eq) were added to the mixture and stirred at 60 °C for 12 hrs. TLC (Petroleum ether/Ethyl acetate = 0/1) showed that compound **4** was consumed and the desired product was detected by LCMS. The mixture was concentrated under reduced pressure to give a residue, which was added water (100 mL). The product was extracted with DCM (50 mL x 3). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 1/1 to 0/1). The desired product compound **6** (4.0 g, 6.57 mmol, 54% yield) was obtained as a yellow solid. LC-MS (m/z): $[M + H]^+ = 642.40$.

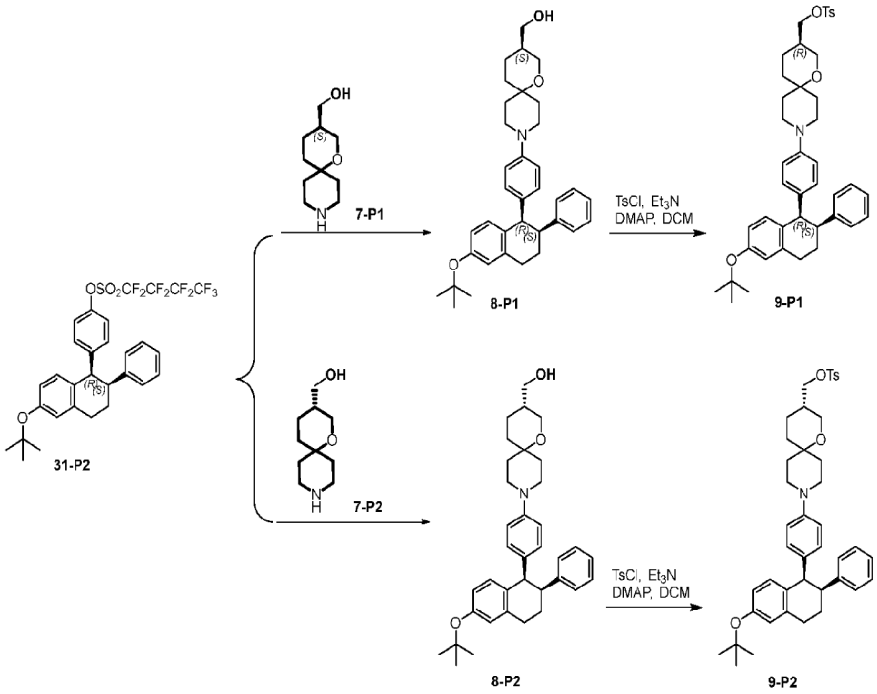
Step 4:

[0893] Add compound **6** (660 mg, 1 mmol, 1 eq), Bu_3SnH (1228 mg, 4 mmol) and AIBN (16.4 mg, 0.1 mmol, 0.1 eq) in toluene (5 mL) at 25 °C and then stir the mixture at 110 °C for 12 h. After the reaction completed, the mixture was quenched by addition saturated potassium fluoride solution and stirred for 1h. The product was extracted with EtOAc. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel to afford the title compound **7** as a yellow solid (400 mg, 69% yield). LC-MS: $[M+H]^+$: 564; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.40 (d, *J* = 7.6 Hz, 1H), 7.39 – 7.29 (m, 5H), 7.18 (d, *J* = 7.6 Hz, 1H), 6.52 (brs, 1H), 5.67 (brs, 1H), 5.16 (s, 2H), 4.89 (m, 1H), 4.52 (s, 2H), 4.48 (d, *J* = 17.3 Hz, 1H), 4.38 (d, *J* = 17.3 Hz, 1H), 4.20 (m, 2H), 2.95 (m, 2H), 2.40 – 2.06 (m, 4H), 1.88 (m, 2H), 1.74 (m, 2H), 1.40 (s, 9H).

Step 5:

[0894] A 2,2,2-Trifluoroethanol solution of the **7** (500 mg) from Step 4 was added palladium on activated carbon catalyst (0.15 eq., 10% purity) under nitrogen. The suspension was degassed

under vacuum and purged with hydrogen three times.The mixture was heated at 25°C for 3h, then filtered and concentrated in vacuo. The residue (**8**) was used directly for next step. LC-MS: [M+H] $^{+}$: 430.



Step 1:

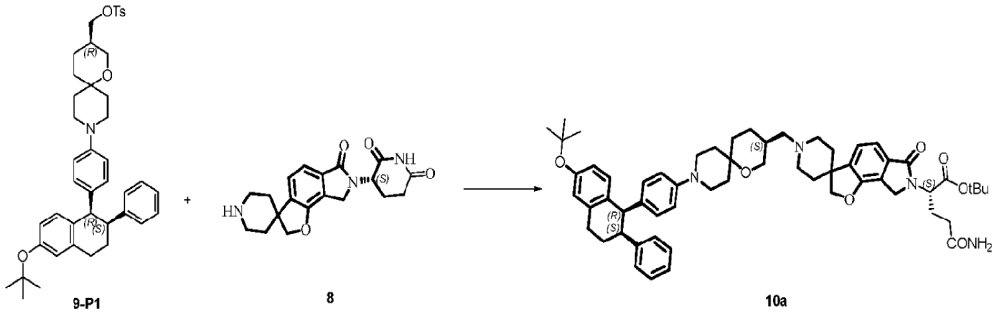
[0895] A round bottomed flask equipped with a stirrer bar was charged with a mixture of compound **31-P2** (650 mg, 1 mmol), chiral amine **7-P1** (222 mg, 1.2 mmol), cesium carbonate (650 mg, 2 mmol), and t-BuXphoxPd-G(III) (*CAS: 1447963-75-8*, 80 mg, 0.1 mmol). The flask was evacuated and back-filled with nitrogen (x 3). *t*-Amyl alcohol (10 mL) was added and the mixture stirred at 100 °C for 10 hours. The cooled reaction mixture was diluted with EtOAc and filtered through Celite™ to remove insoluble material. The filtrate was washed with water, saturated aqueous sodium chloride and then dried over magnesium sulfate, filtered and the filtrate concentrated. The crude material was purified by flash silica chromatography, elution gradient MeOH in DCM. Pure fractions were combined and concentrated to afford compound **8-P1** (135 mg, 25%). LC-MS: [M+H] $^{+}$: 540.

[0896] According to the same procedure, chiral amine **7-P2** was applied to afford compound **8-P2**, LC-MS: [M+H] $^{+}$: 540.

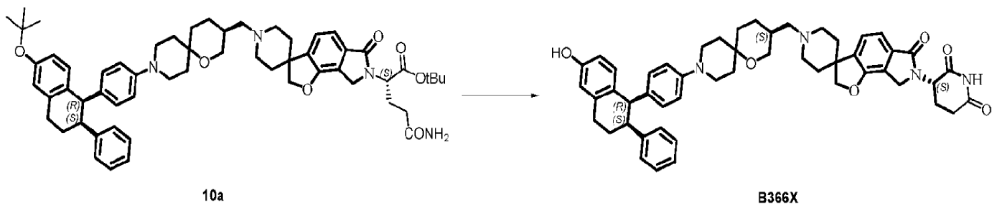
Step 2:

[0897] To a solution of compound **8-P1** (185 mg, 0.34 mmol, 1 eq.) in DCM (5 mL) was added TEA (0.68 mmol, 2 eq.) and DMAP (0.04 mmol, 0.2 eq.). The flask was evacuated and back-filled with nitrogen. TsCl (0.51 mmol, 1.5 eq.) was added and the mixture stirred at R.T. overnight. TLC indicated the starting material was consumed completely. The reaction mixture was quenched by addition of saturated NH_4Cl solution, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by flash silica chromatography to give compound **9-P1** (141 mg, 60%). LC-MS: $[M+H]^+$: 694.

[0898] According to the same procedure, the title compound **9-P2** was provided as a white solid. LC-MS: $[M+H]^+$: 694.

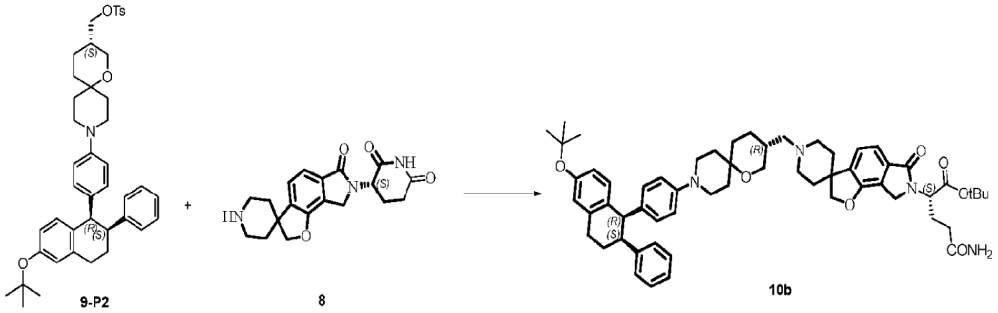


[0899] To a solution of compound **9-P1** (160 mg, 0.235 mmol, 1 eq.) in acetonitrile (2 mL) was added **8** (111 mg, 0.258 mmol, 1.1 eq.), KI (40 mg, 0.235 mmol, 1.0 eq.) and diisopropylethylamine (0.12 mL, 3 eq.). The mixture was stirred at 90 °C for 24 hours. LC-MS showed the reaction was completed. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers was washed wash brine, dried with anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuum. The residue was purified was purified by flash silica chromatography (DCM:MeOH = 10:1) to give the title compound **10a** (155 mg, 70%), LC-MS: $[M+H]^+$: 951.5.

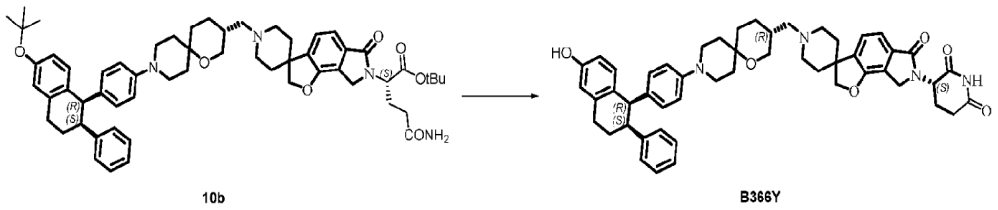


[0900] To a solution of compound **10a** (100 mg, 0.11 mmol, 1 eq.) in acetonitrile (3 mL) was added benzenesulfonic acid (70 mg, 0.44 mmol, 4 eq.). The mixture was stirred at 80 °C for 3 hours. LC-MS showed the reaction was completed. The mixture was concentrated in vacuum. The

residue was purified by preparative reverse phase HPLC (ACN:H_2O = 25-55% (1‰ TFA) to provide the title compound **B366X** (53 mg, 60 %). LC-MS: $[M+H]^+$: 821.4.

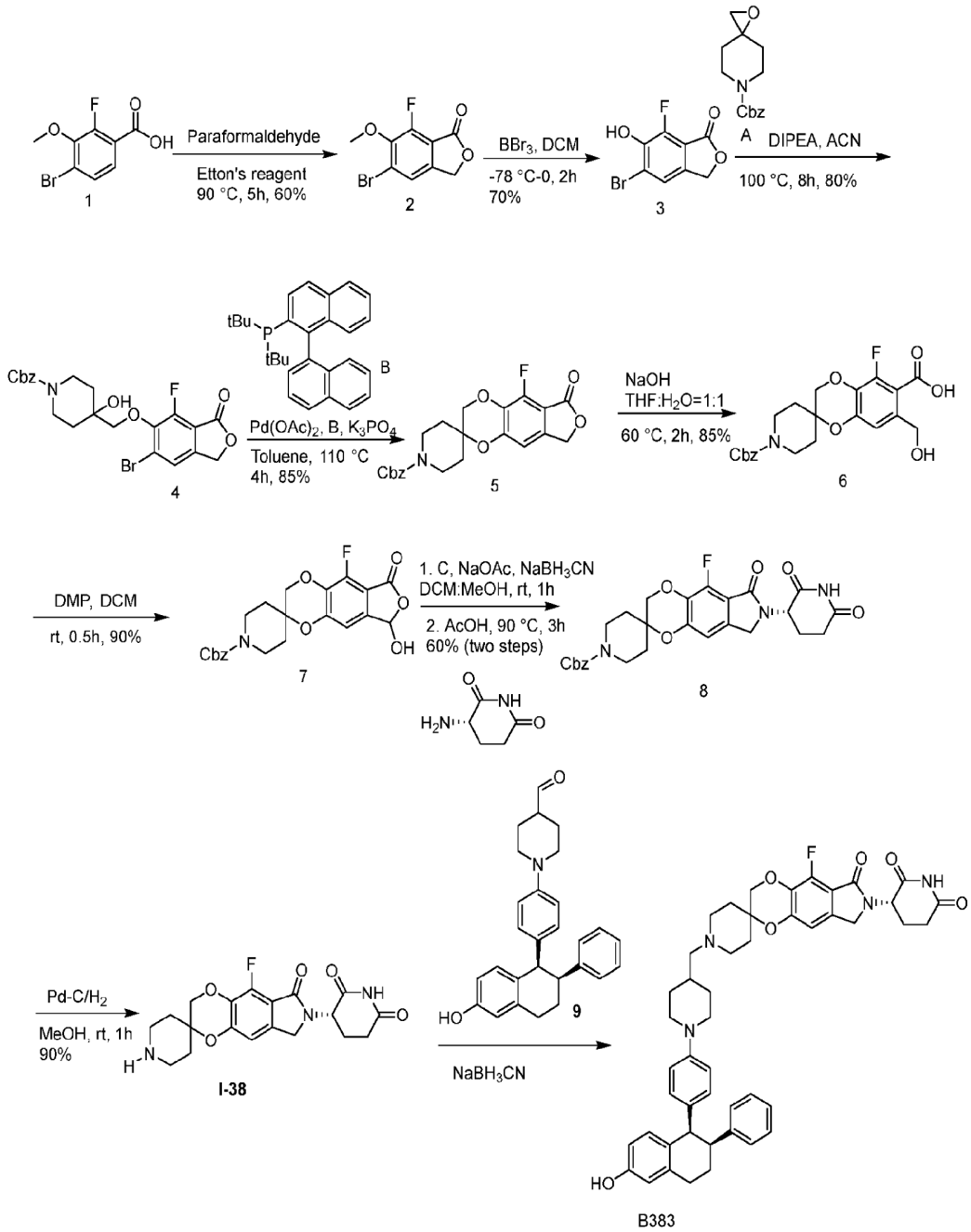


[0901] To a solution of compound **9-P2** (160 mg, 0.235 mmol, 1 eq.) in acetonitrile (2 mL) was added **8** (111 mg, 0.258 mmol, 1.1 eq.), KI (40 mg, 0.235 mmol, 1.0 eq.) and diisopropylethylamine (0.12 mL, 3 eq.). The mixture was stirred at 90 °C for 24 hours. LC-MS showed the reaction was completed. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers was washed wash brine, dried with anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuum. The residue was purified was purified by flash silica chromatography (DCM:MeOH = 10:1) to give the title compound **10b**, LC-MS: $[M+H]^+$: 951.5.



To a solution of compound **10b** (100 mg, 0.11 mmol, 1 eq.) in acetonitrile (3 mL) was added benzenesulfonic acid (70 mg, 0.44 mmol, 4 eq.). The mixture was stirred at 80 °C for 3 hours. LC-MS showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by preparative reverse phase HPLC (ACN:H_2O = 25-55% (1‰ TFA) to provide the title compound **B366Y** (53 mg, 60 %). LC-MS: $[M+H]^+$: 821.4.

Compound B383. (S)-3-(5'-fluoro-1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-6'-oxo-6',8'-dihydro-3'H,7'H-spiro[piperidine-4,2'-[1,4]dioxino[2,3-f]isoindol]-7'-yl)piperidine-2,6-dione.



Step 1: 5-bromo-7-fluoro-6-methoxyisobenzofuran-1(3H)-one:

[0902] To a 100 mL round-bottom flask, Eaton's reagent (30 mL), compound 4-bromo-3-methoxybenzoic acid (**1**, 5 gm, 21.83 mmol) and Paraformaldehyde (1.96 g, 65 mmol) were added in an icc bath. The resulting mixture was stirred and heated to 50 °C for overnight. After being cooled to room temperature, the reaction mixture was poured into ice-cold water (100 mL) and extracted with dichloromethane (3× 60 mL). The combined organic layer was washed with water,

saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo, followed purification by silica gel chromatography to give compound **2** in 70% yield.

Step 2: 5-bromo-7-fluoro-6-hydroxyisobenzofuran-1(3H)-one:

[0903] Over a solution of 5-bromo-6-methoxyisobenzofuran-1(3H)-one (2 g, 8.29 mmol) in dry CH_2Cl_2 (36 mL) under N_2 atmosphere at -20 °C was added boron tribromide (16.6 mL 1M DCM, 16.6 mmol). Then the solution was stirred at rt for overnight. Next, the reaction was quenched adding a saturated solution of $NaHCO_3$ (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3×30 mL), and the organic phases were combined, dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The reaction crude was purified by flash chromatography (20% EtOAc/hexane) affording **3** as a white solid (1.32 g, 70% yield).

Step 3: benzyl 4-(((6-bromo-4-fluoro-3-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-4-hydroxypiperidine-1-carboxylate:

[0904] To a solution of **3** (1 eq.) in DMF (5 mL/mmol), 10 eq. of DIPEA and 1.5 eq. of epoxide were added into the flask. The reaction was heated to 100°C. The reaction was monitored by UPLC-MS. Concentrated directly and purify by silica gel chromatography to give **4** (96% yield). LC/MS (ESI) m/z: 494.09 (M+H)

Step 4: benzyl 5'-fluoro-6'-oxo-6',8'-dihydro-3'H-spiro[piperidine-4,2'-[1,4]dioxino[2,3-f]isobenzofuran]-1-carboxylate:

[0905] To a solution of **4** (1 eq.) in toluene (5 mL/mmol), $Pd(OAc)_2$ (0.1 eq.), [1,1'-binaphthalen]-2-yldi-tert-butylphosphane (0.1 eq.) and K_3PO_4 (3 eq.) was added into the flask under N_2. The reaction was heated to 140 °C under N_2 for 4h. TLC showed reaction was completed. Quenched with saturated $NaHCO_3$, the organic phase was separated. Ethyl acetate was added to the mixture, the resulting mixture was washed by brine. The combined organic phase was dried by $MgSO_4$. Filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give **5** in (70% yield). LC/MS (ESI) m/z: 414.12 (M+H)

Step 5: 1'-((benzyloxy)carbonyl)-5-fluoro-7-(hydroxymethyl)-3H-spiro[benzo[b][1,4]dioxine-2,4'-piperidine]-6-carboxylic acid:

[0906] To a solution of (S)-2-((benzyloxy)methyl)-2,3-dihydro-[1,4]dioxino[2,3-f]isobenzofuran-6(8H)-one (**5**, eq.) in tetrahydrofuran and water (1:1) was added sodium hydroxide (5 eq.). The mixture was stirred at 20 °C for 16 h. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The mixture was adjusted to pH = 5 with aq. hydrochloric acid (1 M) and extracted with

ethyl acetate (10 mL x 3). The organic layer was washed with brine (10 x 2 mL) and dried over sodium sulfate. The crude material (**6**) was not further purified and used as crude for the next steps. LC/MS (ESI) m/z: 432.12 (M+H)

Step 6: benzyl 5'-fluoro-8'-hydroxy-6'-oxo-6',8'-dihydro-3'H-spiro[piperidine-4,2'-[1,4]dioxino[2,3-f]isobenzofuran]-1-carboxylate:

[0907] To a solution of **6** (1.0 eq) in DCM (10 mL) was added DMP (1.2 eq.) at 0 °C and stirred it for 30 mins. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The reaction mixture was then diluted with DCM, washed with brine, dried over and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **7** in (70% yield). LC/MS (ESI) m/z: 430.12 (M+H).

Step 7&8: benzyl (S)-7'-(2,6-dioxopiperidin-3-yl)-5'-fluoro-6'-oxo-7',8'-dihydro-3'H,6'H-spiro[piperidine-4,2'-[1,4]dioxino[2,3-f]isoindole]-1-carboxylate:

[0908] A mixture of **7** (1.0 eq, (S)-3-aminopiperidine-2,6-dione (1.5 eq) and NaOAc (3 eq) was dissolved in methanol:DCM (1:1), and kept stirring at rt for 20 min. Then $NaBH_3CN$ (2.0 eq) was added. 2 h Later, UPLC-MS showed the starting material **7** was completely conversion and a new main peak **8** with desired MS formed. LC/MS (ESI) m/z: 542.16 (M+H). The crude compound **8** (1.0 eq., 440 mg) was dissolved in CH_3CN (4 mL) and was treated with HOAc (15 eq.). The rection was heated at 60 °C and stirred for 2h. Next, the reaction mixture was quenched with water and concentrated under reduced pressure to give a residue which was purified by pre-HPLC to give **8** in (70% yield). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.02 (s, 1H), 7.47 – 7.32 (m, 5H), 6.81 (s, 1H), 5.18 (s, 3H), 4.48 – 4.20 (m, 2H), 4.02 (s, 2H), 3.33 (t, J = 12.5 Hz, 2H), 3.05 – 2.75 (m, 4H), 2.45 – 2.15 (m, 2H), 1.85 (s, 2H), 1.67 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.47, 169.73, 166.88, 155.37, 149.27, 147.61, 146.68, 136.42, 134.67, 131.63, 131.50, 128.56 (two peaks), 128.19, 127.99 (two peaks), 112.12, 112.02, 107.52, 72.74, 70.78, 67.52, 51.79, 46.71, 39.06, 31.44, 23.24. LC/MS (ESI) m/z: 523.15 (M+H).

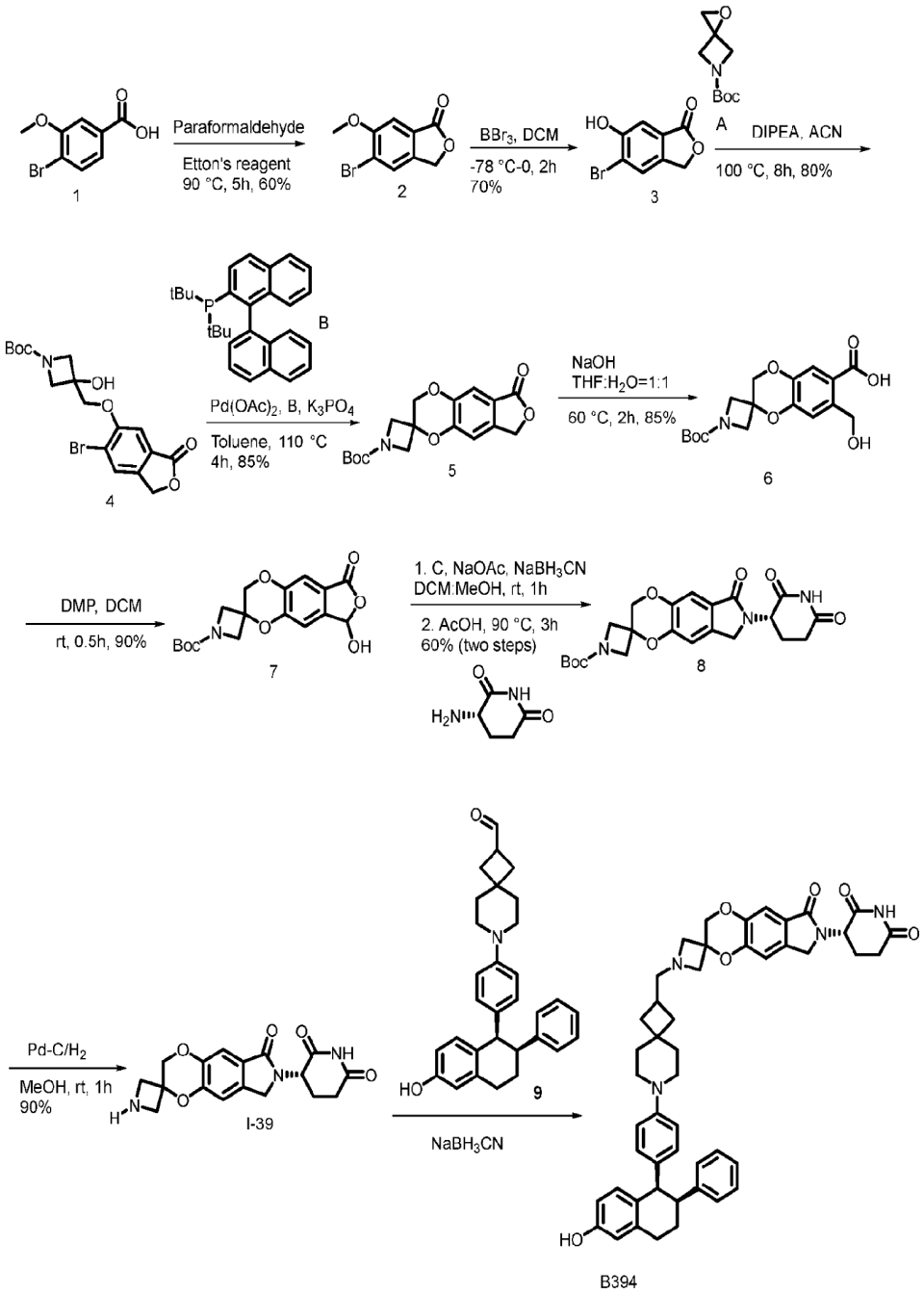
Step 9: (S)-3-(5'-fluoro-6'-oxo-6',8'-dihydro-3'H,7'H-spiro[piperidine-4,2'-[1,4]dioxino[2,3-f]isoindol]-7'-yl)piperidine-2,6-dione:

[0909] To a stirred solution of compound **8** in methanol at room temperature Pd-C was added and the reaction was stirred for another 1 h. UPLC mass chromatography showed the completion of the reaction. Catalyst was filtered out and washed with MeOH. Organic solvent was evaporated, and the product (I-38) was used for the next step. LC/MS (ESI) m/z: 390.12 (M+H)

Step 10: (S)-3-(5'-fluoro-1-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-6'-oxo-6',8'-dihydro-3'H,7'H-spiro[piperidine-4,2'-[1,4]dioxino[2,3-f]isoindol]-7'-yl)piperidine-2,6-dione:

[0910] To a solution of I-38 (1.2 equiv) in Methanol:DCM (4:1) was added NaOAc (2 equiv) and the mixture was stirred at room temperature for 5 mins. The aldehyde 9 (1 equiv) in MeOH: DCM (4:1) was then added to the reaction mixture and stirred for another 10 mins. Sodiumcyanoborohydride (2 equiv) and Acetic acis was then added to the reaction sequentialy and stirred for another 15 minutes. UPLC chromatography showed the completion of the reaction, and the product was purified using preparative HPLC. LC/MS (ESI) m/z: 785.41 (M+H)

Compound B394. (S)-3-(1-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6'-oxo-6',8'-dihydro-3'H,7'H-spiro[azetidine-3,2'-[1,4]dioxino[2,3-f]isoindol]-7'-yl)piperidine-2,6-dione.



Step 1: 5-bromo-6-methoxyisobenzofuran-1(3H)-one:

[0911] To a 100 mL round-bottom flask, Eaton's reagent (30 mL), compound 4-bromo-3-methoxybenzoic acid (**1**, 5 gm, 21.83 mmol) and Paraformaldehyde (1.96 g , 65 mmol) were added in an ice bath. The resulting mixture was stirred and heated to 50 °C for overnight. After being cooled to room temperature, the reaction mixture was poured into ice-cold water (100 mL) and extracted with dichloromethane (3× 60 mL). The combined organic layer was washed with water,

saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo, followed purification by silica gel chromatography to give compound **2** in 70% yield.

Step 2: 5-bromo-6-hydroxyisobenzofuran-1(3H)-one:

[0912] Over a solution of 5-bromo-6-methoxyisobenzofuran-1(3H)-one (2 g, 8.29 mmol) in dry CH_2Cl_2 (36 mL) under N_2 atmosphere at -20 °C was added boron tribromide (16.6 mL 1M DCM, 16.6 mmol). Then the solution was stirred at rt for overnight. Next, the reaction was quenched adding a saturated solution of $NaHCO_3$ (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3×30 mL), and the organic phases were combined, dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The reaction crude was purified by flash chromatography (20% EtOAc/hexane) affording **3** as a white solid (1.32 g, 70% yield).

Step 3: tert-butyl 3-(((6-bromo-3-oxo-1,3-dihydroisobenzofuran-5-yl)oxy)methyl)-3-hydroxyazetidine-1-carboxylate:

[0913] To a solution of **3** (1 eq.) in DMF (5 mL/mmol), 10 eq. of DIPEA and 1.5 eq. of epoxide were added into the flask. The reaction was heated to 100°C. The reaction was monitored by UPLC-MS. Concentrated directly and purify by silica gel chromatography to give **4** (96% yield). LC/MS (ESI) m/z: 414.12 (M+H)

Step 4: tert-butyl 6'-oxo-6',8'-dihydro-3'H-spiro[azetidine-3,2'-[1,4]dioxino[2,3-f]isobenzofuran]-1-carboxylate:

[0914] To a solution of **4** (1 eq.) in toluene (5 mL/mmol), $Pd(OAc)_2$ (0.1 eq.), [1,1'-binaphthalen]-2-yldi-tert-butylphosphane (0.1 eq.) and K_3PO_4 (3 eq.) was added into the flask under N_2. The reaction was heated to 140 °C under N_2 for 4h. TLC showed reaction was completed. Quenched with saturated $NaHCO_3$, the organic phase was separated. Ethyl acetate was added to the mixture, the resulting mixture was washed by brine. The combined organic phase was dried by $MgSO_4$. Filtered and concentrated in vacuum. The residue was purified by silica gel chromatography to give **5** in (70% yield). LC/MS (ESI) m/z: 334.15 (M+H)

Step 5: 1-(tert-butoxycarbonyl)-7'-(hydroxymethyl)-3'H-spiro[azetidine-3,2'-benzo[b][1,4]dioxine]-6'-carboxylic acid:

[0915] To a solution of (S)-2-((benzyloxy)methyl)-2,3-dihydro-[1,4]dioxino[2,3-f]isobenzofuran-6(8H)-one (**5**, 1 eq.) in tetrahydrofuran and water (1:1) was added sodium hydroxide (5 eq.). The mixture was stirred at 20 °C for 16 h. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The mixture was adjusted to pH = 5 with aq. hydrochloric acid (1 M) and extracted with

ethyl acetate (10 mL x 3). The organic layer was washed with brine (10 x 2 mL) and dried over sodium sulfate. The crude material (**6**) was not further purified and used as crude for the next steps. LC/MS (ESI) m/z: 352.12 (M+H)

Step 6: tert-butyl 8'-hydroxy-6'-oxo-6',8'-dihydro-3'H-spiro[azetidine-3,2'-[1,4]dioxino[2,3-f]isobenzofuran]-1-carboxylate:

[0916] To a solution of **6** (1.0 eq) in DCM (10 mL) was added DMP (1.2 eq.) at 0 °C and stirred it for 30 mins. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The reaction mixture was then diluted with DCM, washed with brine, dried over and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **7** in (70% yield). LC/MS (ESI) m/z: 350.15 (M+H).

Step 7&8: tert-butyl (S)-7'-(2,6-dioxopiperidin-3-yl)-6'-oxo-7',8'-dihydro-3'H,6'H-spiro[azetidine-3,2'-[1,4]dioxino[2,3-f]isoindole]-1-carboxylate:

[0917] A mixture of **7** (1.0 eq), (S)-3-aminopiperidine-2,6-dione (1.5 e eq) and NaOAc (3.0 eq) was dissolved in methanol:DCM (1:1), and kept stirring at rt for 20 min. Then $NaBH_3CN$ (2.0 eq.) was added. 2 h Later, UPLC-MS showed the starting material **7** was completely conversion and a new main peak **8** with desired MS formed. LC/MS (ESI) m/z: 462.16 (M+H). The crude compound **8** (1.0 eq) was dissolved in CH_3CN (4 mL) and was treated with HOAc (15 eq.). The rection was heated at 60 °C and stirred for 2h. Next, the reaction mixture was quenched with water and concentrated under reduced pressure to give a residue which was purified by pre-HPLC to give **I-39** in (70% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (s, 1H), 7.43 (s, 1H), 7.01 (d, *J* = 0.8 Hz, 1H), 5.20 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.45 – 4.21 (m, 4H), 4.14 – 3.94 (m, 5H), 3.07 – 2.71 (m, 2H), 2.52 – 2.16 (m, 2H), 1.57 (s, 9H).

[0918] LC/MS (ESI) m/z: 444.15 (M+H).

Step 9: (S)-3-(6'-oxo-6',8'-dihydro-3'H,7'H-spiro[azetidine-3,2'-[1,4]dioxino[2,3-f]isoindol]-7'-yl)piperidine-2,6-dione:

[0919] To a stirred solution of compound **8** in methanol at room temperature Pd-C was added and the reaction was stirred for another 1 h. UPLC mass chromatography showed the completion of the reaction. Catalyst was filtered out and washed with MeOH. Organic solvent was evaporated, and the product (I-39) was used for the next step. LC/MS (ESI) m/z: 344.12 (M+H)

Step 10: (S)-3-(1-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6'-oxo-6',8'-dihydro-3'H,7'H-spiro[azetidine-3,2'-[1,4]dioxino[2,3-f]isoindol]-7'-yl)piperidine-2,6-dione:

[0920] To a solution of I-39 (1.2 equiv) in Methanol:DCM (4:1) was added NaOAc (2 equiv) and the mixture was stirred at room temperature for 5 mins. The aldehyde **9** (1 equiv) in MeOH: DCM (4:1) was then added to the reaction mixture and stirred for another 10 mins. Sodiumcyanoborohydride (2 equiv) and Acetic acis was then added to the reaction sequentialy and stirred for another 15 minutes. UPLC chromatography showed the completion of the reaction, and the product **B394** was purified using preparative HPLC. LC/MS (ESI) m/z: 779.42 (M+H)

Table 7. Characterization Data for "B" Compounds

Compound No.	$(M+H)^+$
B1	681.34
B2	695.32
B3	764.41
B4	736.23
B5	764.34
B6	810.36
B7	792.37
B8	806.32
B9	764.34
B10	778.35
B11	781.92
B12	792.43
B13	739.31
B14	779.34
B15	807.37
B16	843.33
B17	764.04
B18	793.49

Compound No.	$(M+H)^+$
B19	782.51
B20	778.35
B21	778.35
B22	778.35
B23	792.37
B24	792.37
B25	792.37
B26	810.36
B27	810.36
B28	764.12
B29	764.34
B30	792.37
B31	796.34
B32	796.34
B33	796.34
B34	814.34
B35	778.35
B36	757.30
B37	750.32
B38	757.30
B39	820.40
B40	820.40
B41	792.37
B42	792.37
B43	782.33
B44	782.33
B45	825.38
B46	828.35

Compound No.	$(M+H)^+$
B47	798.42
B48	834.40
B49	770.38
B50	820.23
B51	820.05
B52	837.39
B53	810.36
B54	811.35
B55	796.34
B56	806.38
B57	806.38
B58	789.33
B59	761.31
B60	739.31
B61	750.28
B62	764.16
B63	782.13
B64	778.28
B65	750.30
B66	796.17
B67	782.21
B68	782.22
B69	768.19
B70	782.16
B71	754.09
B72	754.32
B73	768.18
B74	782.20

Compound No.	$(M+H)^+$
B75	806.20
B76	778.16
B77	792.14
B78	737.00
B79	778.20
B80	764.26
B81	793.14
B82	794.30
B83	778.20
B84	778.12
B85	794.24
B86	793.04
B87	794.08
B88	792.40
B89	761.15
B90	760.15
B91	760.15
B92	761.04
B93	738.03
B94	752.20
B95	778.28
B96	778.25
B97	778.25
B98	778.07
B99	764.03
B100	764.53
B101	764.25
B102	750.24

Compound No.	$(M+H)^+$
B103	750.23
B104	760.91
B105	778.24
B106	765.12
B107	765.20
B108	764.22
B109	820.24
B110	820.27
B111	792.19
B112	792.17
B113	791.99
B114	806.18
B115	778.30
B116	778.22
B117	759.13
B118	764.23
B119	764.20
B120	822.11
B121	794.15
B122	779.10
B123	779.10
B124	778.14
B125	778.12
B126	779.11
B127	779.13
B128	778.19
B129	778.19
B130	792.23

Compound No.	$(M+H)^+$
B131	792.23
B132	806.21
B133	792.22
B134	765.07
B135	751.95
B136	822.14
B137	765.87
B138	816.40
B139	816.37
B140	849.47
B141	863.48
B142	821.36
B143	821.51
B144	781.47
B145	781.27
B146	849.46
B147	849.45
B148	850.42
B149	851.38
B150	768.25
B151	768.24
B152	807.35
B153	807.38
B154	807.40
B155	807.34
B156	807.36
B157	807.34
B158	850.36

Compound No.	$(M+H)^+$
B159	851.51
B160	821.35
B161	821.37
B162	834.41
B163	750.33
B164	807.34
B165	765.31
B166	778.28
B167	793.36
B168	806.20
B169	806.22
B170	806.34
B171	820.18
B172	808.15
B173	808.14
B174	821.17
B175	807.22
B176	808.10
B177	808.10
B178	807.15
B179	764.34
B180	792.37
B181	764.53
B182	764.37
B183	750.36
B184	736.34
B185	778.35
B186	764.34

Compound No.	$(M+H)^+$
B187	750.32
B188	754.3
B189	749.36
B190	806.38
B191	806.38
B192	778.35
B193	796.34
B194	824.37
B195	808.4
B196	750.36
B197	750.36
B198	778.39
B199	792.4
B200	820.4
B201	806.42
B202	792.4
B203	808.37
B204	767.3
B205	793.32
B206	807.38
B207	767.31
B208	793.41
B209	807.4
B210	808.32
B211	792.4
B212	806.4
B213	820.49
B214	820.33

Compound No.	$(M+H)^+$
B215	738.36
B216	738.34
B217	707.38
B218	821.39
B219	821.39
B220	767.35
B221	821.39
B222	793.36
B223	823.41
B224	741.37
B225	781.40
B226	708.40
B227	708.40
B228	791.41
B229	807.40
B230	780.37
B231	780.42
B232	778.39
B233	778.37
B234	821.43
B235	751.36
B236	797.39
B237	811.41
B238	810.38
B239	810.36
B240	824.39
B242	824.42
B243	752.3

Compound No.	$(M+H)^+$
B244	781.3
B245	767.9
B246	768.3
B247	780.8
B248	768.3
B249	781.3
B250	767.30
B251	793.20
B252	821.20
B253	820.30
B254	821.30
B255	754.20
B256	740.30
B257	740.40
B258	751.40
B259	816.30
B260	792.40
B261	792.30
B262	796.30
B263	750.20
B264	778.30
B265	814.30
B266	796.30
B267	824.40
B268	796.30
B269	824.30
B270	810.40
B271	782.30

Compound No.	$(M+H)^+$
B272	810.30
B273	792.40
B274	764.30
B275	779.30
B276	751.30
B277	779.30
B278	779.30
B279	807.30
B280	810.30
B281	793.30
B282	773.30
B283	806.20
B284	739.30
B285	779.10
B286	779.20
B287	791.30
B288	763.20
B289	763.30
B290	820.30
B291	792.90
B292	804.40
B293	793.30
B294	779.30
B295	766.20
B296	735.30
B297	749.30
B298	752.30
B299	751.30

Compound No.	$(M+H)^+$
B300	751.30
B301	764.30
B302	750.30
B303	778.90
B304	777.40
B305	764.30
B306	752.20
B307	752.10
B308	792.40
B309	792.40
B310	766.40
B311	780.20
B312	794.40
B313	791.30
B314	740.20
B315	712.30
B316	713.30
B317	730.40
B318	805.40
B319	805.30
B320	778.30
B321	778.30
B322	766.40
B323	856.40
B324	842.40
B325	794.30
B326	794.40
B327	796.36

Compound No.	$(M+H)^+$
B328	796.32
B329	806.40
B330	822.40
B331	820.40
B332	822.40
B333	794.40
B334	794.40
B335	793.30
B336	813.35
B337	823.40
B338	767.34
B339	727.36
B340	858.36
B341	796.13
B342	796.11
B343	795.11
B344	739.31
B345	755.41
B346	795.36
B347	785.39
B348	794.40
B349	794.40
B350	809.36
B351	764.36
B352	737.39
B353	766.40
B354	766.30
B355	753.38

Compound No.	$(M+H)^+$
B356	796.42
B358	778.42
B359	777.42
B360	767.36
B362	806.42
B363	806.36
B364	805.43
B365	795.43
B366	821.40
B367	739.25
B368	779.3
B369	766.99
B370	767.24
B371	807.30
B372	823.40
B373	823.31
B374	839.32
B375	739.20
B376	779.35
B377	811.28
B378	701.30
B379	741.30
B380	702.40
B381	742.40
B382	772.40
B383	785.39
B384	825.39
B385	793.35

Compound No.	$(M+H)^+$
B386	809.29
B387	767.19
B388	739.19
B389	873.25
B390	873.44
B391	767.28
B392	767.19
B393	739.19
B394	779.42
B395	767.37
B396	808.41
B397	808.41
B398	808.41
B399	808.41
B400	821.25
B401	821.25

II. BIOLOGICAL ASSAYS

For "A" Compounds

***In vitro* Assay: IC_{50} Measurements for binding to CRBN/DDB1**

[0921] The binding potency was determined using HTRF assay technology (Perkin Elmer). Compounds were serially diluted in DMSO and 0.2 µL volume was transferred to white 384-well plate. The reaction was conducted in total volume of 20 µL with addition of 2 nM His tagged CRBN+DDB-DLS7+CXU4 (Wuxi, catalogue # RP210521GA) to compounds followed by addition of 60 nM Fluorescent probe Cy5-labeled Thalidomide (Tenova Pharma, catalogue # T52461), and 0.4 nM of MAb Anti-6HIS Tb cryptate Gold (Cisbio, catalogue # 61HI2TLA in the assay buffer (50 mM HEPES pH 7.5, 1 mM TCEP, 0.01% Brij-35, 50 mM NaCl, and 0.1% BSA). After one hour incubation at room temperature, the HTRF signals were read on Envision reader

(Perkin Elemer). Data was analyzed using XLfit using four parameters dose response curve to determine IC_{50}s.

Table 8. Binding IC_{50} to CRBN/DDB1

Compound No.	CRBN HTRF IC_{50} (nM)
A1	C
A2	C
A3	D
A4	C
A5	D
A6	C
A7	C
A8	B
A9	A
A10	A
A11	B
A12	B
A13	C
A14	C
A15	C
A16	C
A17	C
A18	C
A19	B
A20	B
A21	B
A22	B
A23	A
A24	B
A25	B
A26	B
A27	B
A28	B
A29	B
A30	B

A31	B
A32	B
A33	B
A34	B
A35	B
A36	A
A37	A
A38	B
A39	B
A40	A
A41	A
A42	B
A43	B
A44	D
A45	D
A46	B
A47	B
A48	B
A49	B
A50	B
A51	B
A52	A
A53	A
A54	A
A55	A
A56	B
A57	B
A58	D
A59	B
A60	B
A61	B
A62	B
A63	C
A64	D
A65	B

A66	B
A67	D
A68	A
A69	B
A70	A
A71	B
A72	B
A73	C
A74	A
A75	A
A76	B
A77	B
A78	A
A79	A
A80	A
A81	A
A82	B
A83	B
A84	B
A85	B
A86	B
A87	B
A88	D
A89	D
A90	D
A91	C
A92	D
A93	A
A94	D
A95	A
A96	B
A97	B
A98	B
A99	B
A100	A

A101	D
A102	A
A103	B
A104	D
A105	B
A106	B
A107	D
A108	C
A109	C
A110	B
A111	D
A112	B
A113	B
A114	ND
A115	ND
A116	A
A117	A
A118	C
A119	B
A120	C
A121	C
A122	B
A123	B
A124	C
A125	B
A126	B
A127	ND
A128	B
A129	B
A130	C
A131	A
A132	C
A133	ND
A134	ND
A135	C

A136	C
A137	B
A138	B
A139	B
A140	A
A141	A
A142	A
A143	C
A144	C
A145	B
A146	B
A147	B
A148	A
A149	C
A150	C
A151	C
A152	C
A153	A
A154	A
A155	B
A156	B
A157	C
A158	C
A159	B
A160	B
A161	A
A162	B
A163	B
A164	C
A165	B
A166	ND
A167	ND
A168	ND
A169	ND
A170	ND

A171	ND
A172	ND

Note: IC_{50}: "A": < 50 nM; "B": 50-500 nM; "C": > 500 and <5000 nM; "D": >=5000 nM; ND: Not determined

***In vitro* Assay: IC_{50} Measurements for binding to ERα_LBD (GST)**

- Final assay conditions:

1. ERα_LBD(GST) protein: 4 nM
2. Tb Anti-GST: 2nM
3. Fluormone ES2 Green tracer: 3nM
4. Incubation time: 60 min
5. DMSO: 1%
6. Assay buffer: Adding 1M DTT to Nuclear receptor Buffer K for final 5mM DTT.
7. ZPE: 1% DMSO
8. HPE: 1μM ARV_471 (positive control)
9. LanthaScreen® TR-FRET ERα Competitive Binding Assay (ThermoFisher, # A15887)

- 100x Compound preparation:

1) Cherry pick 2 μL 10mM compound stock to column 1 of a 384 intermediate plate.
2) Add 18 μL DMSO to column 1 to dilute compound to 1mM.
3) Transfer 10 μL 1mM compound to column 1 of a LDV plate.
2) Add 6μl DMSO to column 2-10 of the LDV plate.
3) Compounds undergo 3-fold serial dilution (3 μL+6 μL) in DMSO.
4) Transfer 120 nL compound solution to assay plate.

ZPE: 120 nL 100% DMSO

- Procedure:

[0922] Complete nuclear receptor buffer K was prepared by adding 1 M DTT to nuclear receptor buffer K for a final concentration of 5 mM DTT. Complete nuclear receptor buffer K must be prepared fresh daily. 2X protein solution was prepared using complete nuclear receptor buffer K containing 8nM ERα_LBD(GST) and 4nM Tb Anti-GST. Then, 2X Fluormone ES2 Green tracer (6 nM) was prepared using complete nuclear receptor buffer K. Add 6 μL 2X Fluormone ES2 green tracer into a compound plate (PerkinElmer 6008289) by dragonfly with one-tips-addition. Subsequently, 6 μL 2X protein solution was added into the plate. The 384-well plate was mixed

on a plate shaker and incubated at room temperature protected from light for 60min. The plate was sealed with a cover to minimize evaporation. The plate was read at wavelengths of 520 nm and 495 nm. The TR-FRET ratio was calculated by dividing the emission signal at 520 nm by the emission signal at 495 nm. A binding curve was generated by plotting the emission ratio vs. the log [ligand]. To determine the IC_{50} value, fit the data using XL-fit for a sigmoidal dose-response.

Table 9. ERα binding IC_{50}

Compound No.	ERα HTRF IC_{50} (nM)
A2	A
A6	A
A9	B
A11	B
A18	C
A24	A
A25	A
A30	A
A31	A
A32	C
A33	A
A35	A
A41	A
A43	A
A52	A
A54	A
A56	A
A68	A
A69	A
A71	A
A72	A
A73	A

Compound No.	ERα HTRF IC_{50} (nM)
A76	A
A77	A
A82	A
A91	A
A94	A
A95	A
A99	A
A100	A
A101	A
A112	A
A116	A
A123	A
A129	A
A131	A
A133	A
A134	A
A135	A
A136	A
A154	A
A161	A
A166	A
A173	A
A174	A
A175	A
A176	A

Note: IC_{50}: "A": < 10 nM; "B": 10-100 nM; "C": >100 nM.

In-cell Western (ICW) assays in MCF-7 and T47D cell lines.

- *Reagents and Consumables for ICW*

1) MCF-7 from HDB
2) T47D from HDB
3) CS-FBS, BI, Cat#04-201-1
4) phenol red-free RPMI1640, Thermo, Cat#11835
5) P/S, Biosera Liquid, Cat#XC-A4122
6) 384-well cell plate(black), Corning, Cat#3764
7) PFA, Electron Microscopy Sciences, Cat#15710
8) Intercept (PBS) Blocking Buffer, Licor, Cat# 927-70001
9) Triton X-100, Sigma, Cat#X-100
10) ER antibody, CST, Cat#13258
11) IRDye 800CW Goat anti-Rabbit IgG, LiCor, Cat#926-32211
12) CellTag 700 Stain, Licor, Cat# 926-41090
13) Odyssey® DLx Imaging System, LiCor
14) EnVision, PerkinElmer

- *MCF-7 and T47D ICW assays*

[0923] Day 1: MCF-7 and T47D cell (From HDB) were seeded in 384-well black plate with phenol red-free RPMI1640 + 10% CS-FBS + 1% P/S medium ($1*10^4$ for MCF-7 and $1.5*10^4$ for T47D cells/well, 30ul medium) for overnight at 37°C, 5%CO_2 incubator.

[0924] Day 2: Cells were treated at desired compound concentrations (0.02 to 300 nM) and DMSO as vehicle control for 16 hrs at 37°C, 5%CO_2 incubator.

[0925] Day 3: After 16 hrs of compounds treatment, cells were fixed by 4% PFA and permeabilized with elution buffer (0.1% Triton X-100 in 1% PBS Solution). Subsequently, cells were blocked with Intercept (PBS) Blocking Buffer (Li-COR, Odyssey Blocking Buffer), and were stained with ER (1:500, Cell signaling) primary antibody for overnight at cold room.

[0926] Day 4: Remove the buffer, add IRDye 800CW Goat anti-Rabbit IgG Secondary Antibody (1:2000) and CellTag 700 Stain (1:500) in Intercept (PBS) Blocking Buffer. Finally, cell plate is placed in incubator to dry. Image and signal were captured on Odyssey® DLx Imaging System. Data was further analyzed using XLfit using four parameters dose response curve to determine DC_{50} and D_{max}.

- *Data analysis*

[0927] Data are analyzed by image studio V5.2 and XLfit.

[0928] Half maximal degradation concentration values (DC_{50}) and maximal degradation percentage (D_{max}, %) of ER are summarized in **Table 10**.

Table 10. ER degradation by in-cell western (ICW) assays

Compound No.	MCF7 DC_{50} (nM)	MCF7 D_{max} (%)	T47D DC_{50} (nM)	T47D D_{max} (%)
A1			B	C
A2	A	A	A	A
A3	A	C		
A4	B	B	A	B
A5	A	B	A	C
A6	A	B	A	B
A7	A	B	A	B
A8	A	A	A	A
A9	B	B	B	B
A10	A	A	A	A
A11	C	B	B	B
A12	A	A	A	A
A13	B	B	B	B
A14	A	B	A	B
A15	C	C	C	C
A16	B	B	A	B
A17	B	C	B	C
A18	A	B	A	B
A19	B	B	B	B
A20	A	B	A	B
A21	C	B	B	B
A22	A	B	A	C
A23	C	C	C	B
A24	A	A	A	A
A25	A	A	A	A
A26	C	C	C	C
A27	C	C	D	D
A28	C	C	C	C
A29	C	C	C	C
A30	A	B	A	A

Compound No.	MCF7 DC_{50} (nM)	MCF7 D_{max} (%)	T47D DC_{50} (nM)	T47D D_{max} (%)
A31	A	B	A	A
A32	C	B	C	B
A33	A	B	A	B
A34	A	A	A	A
A35	A	A	A	A
A36	A	B	A	C
A37	A	C	A	C
A38	C	C	B	C
A39	C	C	B	B
A40	C	C	C	C
A41	A	A	A	A
A42	C	B	C	B
A43	A	B	A	A
A44	D	D	D	D
A45	D	D	D	D
A46	C	C	C	C
A47	C	B	B	C
A48	B	B	B	B
A49	A	B	A	B
A50	A	B	A	B
A51	D	D	D	D
A52	A	B	A	A
A53	C	C	B	B
A54	A	B	A	A
A55	C	C	B	B
A56	A	B	A	A
A57	C	C	B	B
A58	A	A	A	B
A59	A	D	D	D
A60	D	C	D	D
A61	D	D	D	D
A62	C	C	B	C
A64	B	B	B	B

Compound No.	MCF7 DC_{50} (nM)	MCF7 D_{max} (%)	T47D DC_{50} (nM)	T47D D_{max} (%)
A65	B	B	A	A
A66	B	B	B	B
A67	B	B	B	B
A68	A	B	A	A
A69	A	B	A	A
A70	A	B	ND	ND
A71	A	A	ND	ND
A72	A	B	A	A
A73	A	A	A	A
A74	A	B	ND	ND
A75	A	B	ND	ND
A76	A	A	ND	ND
A77	A	B	A	A
A78	A	B	ND	ND
A79	A	B	ND	ND
A80	A	B	ND	ND
A81	A	C	ND	ND
A82	A	A	ND	ND
A83	ND	ND	A	B
A84	A	D	C	C
A85	A	C	A	B
A86	B	D	C	C
A87	A	C	A	C
A88	B	B	A	C
A89	A	C	A	C
A90	A	C	A	C
A91	A	A	A	A
A92	A	C	B	C
A93	A	B	A	B
A94	A	A	A	A
A95	A	A	A	A
A96	A	B	A	B
A97	ND	ND	B	A

Compound No.	MCF7 DC_{50} (nM)	MCF7 D_{max} (%)	T47D DC_{50} (nM)	T47D D_{max} (%)
A98	ND	ND	C	C
A99	A	A	A	A
A100	A	A	A	A
A101	A	A	ND	ND
A102	ND	ND	B	A
A103	ND	ND	C	B
A104	B	B	A	A
A105	A	B	B	B
A106	A	B	A	B
A107	A	B	A	B
A108	A	B	A	B
A109	A	C	A	B
A110	A	B	A	B
A111	B	B	B	A
A112	A	A	ND	ND
A113	C	C	C	C
A114	ND	ND	D	D
A115	ND	ND	B	A
A116	A	B	A	A
A117	C	C	ND	ND
A118	A	C	ND	ND
A119	A	C	A	C
A120	C	C	ND	ND
A121	B	A	ND	ND
A122	A	B	A	B
A123	A	A	A	A
A124	C	B	C	B
A125	ND	ND	C	B
A126	A	B	A	A
A127	B	B	ND	ND
A128	B	B	ND	ND
A129	A	A	A	A
A130	B	A	ND	ND

Compound No.	MCF7 DC_{50} (nM)	MCF7 D_{max} (%)	T47D DC_{50} (nM)	T47D D_{max} (%)
A131	A	A	ND	ND
A132	B	B	ND	ND
A133	A	A	ND	ND
A134	A	A	ND	ND
A135	A	A	A	7A
A136	A	A	A	A
A137	B	D	ND	ND
A138	A	B	ND	ND
A139	B	B	ND	ND
A140	A	A	B	A
A141	B	B	ND	ND
A142	A	B	ND	ND
A143	C	B	ND	ND
A144	B	B	ND	ND
A145	C	B	ND	ND
A146	C	C	ND	ND
A147	A	A	B	A
A148	A	B	A	A
A149	B	A	ND	ND
A150	C	B	ND	ND
A151	C	C	ND	ND
A152	B	B	ND	ND
A153	D	D	ND	ND
A154	A	B	A	A
A155	B	C	C	D
A156	A	A	ND	ND
A157	C	D	ND	ND
A158	A	B	ND	ND
A159	C	C	ND	ND
A160	C	B	ND	ND
A161	A	B	ND	ND
A162	A	C	ND	ND
A163	B	A	ND	ND

Compound No.	MCF7 DC_{50} (nM)	MCF7 D_{max} (%)	T47D DC_{50} (nM)	T47D D_{max} (%)
A164	B	A	ND	ND
A165	C	B	ND	ND
A166	A	B	ND	ND
A167	A	B	ND	ND
A168	B	B	ND	ND
A169	C	C	ND	ND
A170	C	C	ND	ND
A171	A	A	ND	ND
A172	C	C	ND	ND
A173	A	A	A	A
A174	A	A	A	A
A175	A	A	A	A
A176	A	A	A	A
A177	A	A		
A178	A	A		
A179	A	A		
A180	A	A		
A181	A	A		
A182	A	B		
A183	A	B		
A184	A	B		
A185	A	A		
A186	A	B		
A187	A	A		
A188	A	A		
A189	A	A		
A190	A	B		
A191	A	B		
A192	A	A		
A193	A	A		
A194	B	A		
A195	A	A		
A196	A	A		

Compound No.	MCF7 DC_{50} (nM)	MCF7 D_{max} (%)	T47D DC_{50} (nM)	T47D D_{max} (%)
A197	A	A		
A198	A	B		
A199	A	B		
A200	A	A		
A201	A	B		
A202	A	B		
A203	A	A		
A204	B	B		
A205	B	C		
A206	B	B		
A207	A	A		
A208				
A209				
A210	A	A		
A211				
A212				
A213				
A214				
A215				
A216				
A217				
A218	A	A		
A219				
A220				
A221				
A222	A	A		
A223				
A224				
A225				
A226	A	A		
A227	A	A		
A228				
A229	A	A		

Compound No.	MCF7 DC_{50} (nM)	MCF7 D_{max} (%)	T47D DC_{50} (nM)	T47D D_{max} (%)
A230	A	A		
A231	A	A		
A232	A	A		
A233	A	A		
A234	A	A		
A235	A	A		
A236	A	A		

Note: IC_{50}: "A": < 1 nM; "B": 1-10 nM; "C": >10 and <100 nM; "D": >=100 nM.
D_{max}: "A": >=75%; "B": >50 and <75%; "C": 25-50%; "D": <25%.

CellTiter-Glo® (CTG) assays in MCF-7 and T47D cell lines.

- *Reagents and Consumables for CTG*

1) MCF-7 from HDB
2) T47D from HDB
3) CS-FBS, BI, Cat#04-201-1
4) phenol red-free RPMI1640, Thermo, Cat#11835
5) P/S, Biosera Liquid, Cat#XC-A4122
6) 384-well cell plate(white), Corning, Cat#3765
7) Cell TiterGlo reagent, Promega, Cat#G7573
8) EnVision, PerkinElmer

- *Medium*

1) Cell culture medium: phenol red-free RPMI1640+10%CS-FBS,1% P/S

- *Procedures for CTG assay*

In vitro Assay: MCF-7 and T47D CTG assay

[0929] Day-1: MCF-7 and T47D cell (From HDB) were cultured in 384-well white plate with phenol red-free RPMI1640 + 10% CS-FBS + 1% P/S medium (1,000cells/well) for overnight at 37°C, 5%CO_2 incubator.

[0930] Day 0: Cells were treated at desired compound concentrations (0.5 to 10000nM) (DMSO and Staurosporine as control) for Day 6 at 37°C,5%CO_2 incubator.

[0931] Day 0 and Day 6: add Cell TiterGlo reagent and read on EnVision after 30min incubation for data generation.

- *Data analysis*

Data are analyzed by image studio V5.2 and XLfit.

[0932] Half maximal inhibitory concentration values (IC_{50}) of MCF-7 and T47D cell proliferation are summarized in **Table 11**.

Table 11. CellTiter-Glo® (CTG) IC_{50}

Compound No.	MCF7 IC_{50} (nM)	T47D IC_{50} (nM)
A12	B	
A24	B	
A25	A	
A31	B	C
A34	A	A
A35	B	B
A41	A	A
A43	B	B
A65	B	
A68	B	
A71	A	
A72	A	
A73	B	
A76	A	
A77	A	
A100	A	A
A135	A	A
A136	A	A
A173	A	A
A174	A	A
A175	A	A
A176	A	A
A177	C	
A178	C	
A179	C	
A180	C	

A181	C	
A184	C	
A185	C	
A187	B	
A188	B	
A189	B	
A191	B	
A192	C	
A193	B	
A194	C	
A195	C	
A196	A	
A197	B	
A198	B	
A199	A	
A200	A	
A201	C	
A202	C	
A203	A	
A204	C	
A205	C	
A206	C	
A207	C	
A208	B	
A209	A	
A210	A	
A213	A	
A214	A	
A215	A	
A217	A	
A218	A	
A219	A	
A220	A	
A221	C	
A222	A	

A223	A	
A224	B	
A225	A	
A226	A	
A227	A	
A228	B	
A229	B	
A230	A	
A231	A	
A232	A	
A233	A	
A234	A	
A235	A	
A236	B	

Note: IC_{50}: "A": < 10 nM; "B": 10-100 nM; "C": > 100 nM.

For "B" Compounds

[0933] In-cell western blot analysis. a. seed cells in black-sided/clear bottom 96- or 384-well plates at 40,000 or 10,000 cells/well, overnight; b. add diluted compounds (final 0.5% DMSO), 16 hours. 16 h later, remove medium, add 100 µL or 25 µL of 3.7-4.0% formaldehyde (PBS:FA=9:1), RT 20 min, no shaking; c. wash with PBS, and permeabilized with 100 µL or 25 µL/well of 1X PBS + 0.1% Triton X-100 10 minutes; d. block with 100 µL or 25 µL Licor blocking buffer (Li-Cor), RT 1h, moderate shaking; d. Add 100 µL or 25 µL of anti-ER (cs-8644, 1:500-1,000) + GAPDH(Millipore MAB374, 1:1000) in Block + 0.05%Tween 20. RT 2h, gentle shaking. Negative control: cells plus secondary antibodies (no primary antibodies); e. wash x 4 with PBS +0.05-0.1% Tween 20, gentel shaking; f. anti-rabbit-680 and anti-mouse-800 (both 1:1000 in LiCor block +0.05% Tween20, RT 1h, gentle shaking, no light. LI-COR: 0.2% to reduce background; g. wash x 4 with PBS +0.05% Tween 20, gental shaking; h. add 100 µL or 25 µL of PBS to each well and read on CLX plate reader. The relative ER percentage in treated cells were obtained by comparing the values of treated wells to those in untreated and DMSO-treated wells as 100%.

[0934] Western Blot Analysis. Western blot analysis was performed essentially as described previously. The cells treated with indicated compounds were lysed in Radioimmunoprecipitation

Assay Protein Lysis and Extraction Buffer (25 mmol/L Tris.HCl, pH 7.6, 150 mmol/L NaCl, 1% Nonidet P-40, 1% sodium deoxycholate, and 0.1% sodium dodecyl sulfate) containing proteinase inhibitor cocktail (Roche Diagnostics, Mannheim, Germany). Equal amounts of total protein were electrophoresed through 10% SDS-polyacrylamide gels after determination of protein concentration by BCA assay (Fisher Scientific, Pittsburgh, PA). The separated protein bands were transferred onto PVDF membranes (GE Healthcare Life Sciences, Marlborough, MA) and blotted against different antibodies, as indicated. The blots were scanned, and the band intensities were quantified using GelQuant.NET software provided by biochemlabsolutions.com. The relative mean intensity of target proteins was expressed after normalization to the intensity of glyceraldehyde-3-phosphate dehydrogenase bands.

[0935] Cell Growth Assay. The cells were seeded at 1500/well in 96 well plates overnight. One day after the seeding, they were treated with indicated doses of compounds respectively. 4 days after the compound treatment, 10% WST-8 reagent was added to the culture medium and incubate in a CO2 incubator at 37°C for 2.5 hours. Before reading, the plate was mixed gently on an orbital shaker for one minute to ensure homogeneous distribution of color. The absorbance was measured of each sample using a microplate reader at a wavelength of 450 nm. The relative absorbance was calculated against the vehicle control from three individually repeats.

[0936] In vivo pharmacodynamic and efficacy studies. To develop breast cancer cell line xenografts, mice was given 4 ug/ml 17β-Estradiol in 0.05% ETOH dringking water for 1 week, followed with 8 ug/ml 17β-Estradiol in 0.1% EtOH drinking water thereafter. Five million cells in 50% Matrigel were injected subcutaneously into SCID mice. when tumors reached 100–400 mm^3, mice were treated with vehicle control (5%DMSO, 10%solutol, 85%Water) or indicated dose of the drugs, sacrificed at indicated time-points, and tumor tissue was harvested for analysis. For in vivo efficacy experiments, when tumors reached 80–200 mm3, mice were randomized into groups. vehicle control (5%DMSO, 10%solutol, 85%Water) was given at the dose and with the duration indicated. Tumor sizes and animal weights were measured 2–3 times per week. Tumor volume (mm^3) = (length × width2)/2. Tumor growth inhibition was calculated as TGI (%) = (Vc−Vt)/(Vc−Vo) × 100, where Vc, Vt are the median of control and treated groups at the end of the study and Vo at the start. All the in vivo studies were performed under an animal protocol (PRO00005315) approved by the University Committee on Use and Care of Animals of the

University of Michigan, in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health.

Table 12. Biological Data for Compounds B1 to B401

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B1	C		
B2	B		
B3	A		
B4	B		
B5	A		C
B6	A		
B7	A		
B8	B		
B9	B		
B10	B		
B11	A		
B12	B		C
B13	C		
B14	C		
B15	B		
B16	B		
B17	B		
B18	B		
B19	B		
B20	B		
B21	C		
B22	C		
B23	B		C
B24	B		C

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B25	C		
B26	B		
B27	C		
B28	A		B
B29	C		
B30	C		C
B31	C		
B32	C		
B33	C		
B34	C		
B35	B		
B36	C		
B37	C		
B38	C		
B39	C		
B40	C		
B41	C		
B42	C		
B43	C		B
B44	B		C
B45	C		C
B46	C		C
B47	B		B
B48	B		B
B49	B		B
B50	B		C
B51	C		NA

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B52	C		B
B53	C		
B54	C		
B55	B		
B56	B		B
B57	C		B
B58	C		
B59	C		
B60	C		
B61	A		
B62	B		
B63	C		
B64	A		B
B65	C		
B66	B		
B67	C		
B68	A		
B69	C		
B70	C		
B71	C		
B72	B		
B73	C		
B74	C		
B75	C		
B76	B		
B77	C		
B78	C		

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B79	C		
B80	C		
B81	C		
B82	C		
B83	B		
B84	C		
B85	C		
B86	C		
B87	C		
B88	C		
B89	C		
B90	C		
B91	B		
B92	C		
B93	C		
B94	C		
B95	C		
B96	C		
B97	C		
B98	C		
B99	C		
B100	C		
B101	C		
B102	C		
B103	C		
B104	C		
B105	A		

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B106	A		
B107	C		
B108	B		
B109	A		
B110	C		
B111	C		
B112	A		
B113	B		
B114	C		
B115	C		
B116	C		
B117	C		
B118	C		
B119	C		
B120	C		
B121	B		
B122	B		
B123	A		
1B24	C		
B125	A		
B126	B		
B127	C		
B128	B		
B129	C		
B130	C		
B131	C		
B132	C		

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B133	B		B
B134	C		
B135	B		B
B136	B		B
B137	B		
B138	C		B
B139	B		
B140		A	A
B141		A	A
B142		A	A
B143		A	A
B144		B	A
B145		B	A
B146		A	A
B147		B	B
B148		B	B
B149		B	A
B150		A	A
B151		A	A
B152		A	A
B153		A	A
B154		A	A
B155		A	A
B156		C	
B157		B	A
B158		B	
B159		B	B

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B160		A	
B161		A	
B162		B	
B163		A	B
B164		A	B
B165		C	A
B166		A	A
B167		A	A
B168		A	A
B169		A	
B170		A	A
B171		A	A
B172		B	A
B173		C	A
B174		C	A
B175		B	A
B176		B	B
B177		C	B
B178		C	A
B179	C		
B180	C		
B181	C		
B182	B		
B183	A		
B184	A		
B185	B		
B186	B		

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B187	B		
B188	B		
B189	C		
B190	C		
B191	B		
B192	B		
B193	B		
B194	B		
B195	B		
B196	B		
B197	B		
B198	B		
B199	C		
B200	B		
B201	B		
B202	C		
B203		A	A
B204		A	A
B205		A	B
B206		A	A
B207		A	A
B208		A	A
B209		A	A
B210		A	A
B211		A	B
B212		A	A
B213		A	A

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B214		A	A
B215		B	B
B216		B	C
B217		C	B
B218		C	A
B219		B	A
B220		C	A
B221		B	A
B222		B	A
B223		B	C
B224		C	B
B225		B	B
B226		A	A
B227		A	A
B228		A	B
B229		B	B
B230		A	A
B231		B	A
B232		C	B
B233		C	B
B234		C	A
B235		C	B
B236		B	A
B237		C	B
B238		A	A
B239		B	B
B240		A	B

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B242		A	A
B243		B	B
B244		B	A
B245		B	A
B246		A	A
B247		B	A
B248		B	A
B249		B	A
B250		B	A
B251		A	A
B252		A	A
B253		A	A
B254		B	A
B255		B	B
B256		B	B
B257		C	B
B258		B	A
B259	B		
B260	C		
B261	C		
B262	C		
B263	C		
B264	C		
B265	C		
B266	C		
B267	C		
B268	C		

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B269	C		
B270	C		
B271	C		
B272	B		
B273	C		
B274	C		
B275	C		
B276	C		
B277	C		
B278	C		
B279	C		
B280	C		
B281	B		
B282	C		
B283	C		
B284	C		
B285	B		
B286	C		
B287	C		
B288	C		
B289	C		
B290	C		
B291	C		
B292	C		
B293	B		
B294	A		
B295	C		

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B296	C		
B297	C		
B298	B		
B299	C		
B300	C		
B301	C		
B302	C		
B303	C		
B304	C		
B305	C		
B306		C	A
B307		C	B
B308		A	A
B309		A	
B310		C	A
B311		C	A
B312		C	A
B313		B	A
B314		C	B
B315		C	B
B316		B	B
B317		C	B
B318		C	
B319		C	
B320		C	
B321		C	
B322		A	

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B323	C		
B324	C		
B325		B	B
B326		C	B
B327		B	A
B328		B	B
B329		C	C
B330		A	A
B331		C	
B332		A	B
B333		A	A
B334		B	A
B335		B	A
B336		B	B
B337		A	A
B338		B	B
B339		C	B
B340		B	B
B341		A	A
B342		A	B
B343		C	B
B344		C	B
B345		C	B
B346		B	B
B347		B	A
B348		A	
B349		B	

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B350		B	C
B351		A	B
B352		B	B
B353		B	
B354		B	
B355		B	A
B356		A	B
B358		B	C
B359		B	B
B360		C	C
B362		B	C
B363		B	C
B364		C	B
B365		B	C
B366		A	A
B367		C	B
B368		C	B
B369		B	A
B370		C	B
B371		A	A
B372		B	B
B373		A	A
B374		A	A
B375		B	A
B376		B	A
B377		B	A
B378		C	

Compound No.	Traditional Western Degradation Potency (DC_{50})	ICW DC_{50} (nM)	Cell growth Inhibition in T47D cell line IC_{50} (nM)
B379		C	
B380		C	
B381		C	
B382		C	
B383		C	C
B384		C	B
B385		C	B
B386		C	B
B387		C	B
B388			A
B389		C	C
B390		B	C
B391		C	B
B392			B
B393			A
B394			B
B395			B
B396		A	A
B397		A	A
B398		A	A
B399		A	A
B400		A	A
B401		A	A

Note:
DC_{50}: "A": < 10 nM; "B": 10-100 nM; "C": > 100 nM.
IC_{50}: "A": < 1 nM; "B": 1-10 nM; "C": > 10 nM.

***In vitro* efficacy studies**

ER degradation in breast cancer cell lines

[0937] ER degradation is measured using several different breast cancer cell lines in multiple cellular assays. Cell lines to be used for this purpose include, but are not limited to, MCF-7 cells (ATCC, catalog # HB-22), T47D cells (ATCC, catalog # HTB-133), or CAMA1 cells (ATCC, catalog # HTB-21) expressing wild type ER, or breast cancer cell lines expressing clinically relevant ER gene mutations, such as MCF-7 cells engineered to express Q380E, Y537S, or D538G ER. Endogenous ER in breast cancer cell lines is measured using Western blot, in-cell Western assay or HiBiT assay in cells engineered to express a HiBiT-tagged version of ER. ER degradation is measured at times, e.g., between 2 and 24 hours. Cells are treated with vehicle control (DMSO) or the compound at various concentrations (e.g., ranging from 0.005 nM to 100 nM). Some assays are conducted in the presence of estradiol, while other assays are conducted in the absence of estradiol. The compounds of this disclosure are expected to degrade ER protein in breast cancer cell lines.

Cell growth inhibition in breast cancer cell lines

[0938] Cell growth inhibition is measured using several different cell lines (e.g., the ones mentioned above) to test whether ER degradation with the compounds of this disclosure impacts cell growth inhibition in breast cancer cell lines. Cells are treated with vehicle control (DMSO) or the compound at various concentrations (e.g., ranging from 0.003 nM to 100 nM) for about 144 hours. Briefly cells per well are plated in each well of a 384-well plate. 24 hours later, the compound is dispensed into the wells. 144 hours after compound is added to wells, CellTiter-Glo (Promega) is added to wells and plates are read on an EnVision® Plate Reader (Perkin Elmer). The compounds of this disclosure are expected to inhibit or retard cell growth in breast cancer cell lines.

In vivo Pharmacokinetic and Pharmacodynamic (PKPD) and efficacy studies

ER degradation in MCF-7 tumor model

[0939] To evaluate the ability of compounds of this disclosure to reduce ER protein levels *in vivo*, an orthotopic human breast cancer MCF7 xenograft model in female NOD/SCID mice is used. Each mouse is implanted subcutaneously with estrogen pellets at the right flank before the tumor inoculation. Each mouse is inoculated at the right third mammary fat pad with MCF7 tumor cells (2×10^7) in 0.2 mL of PBS with Matrigel (1:1) for tumor development. Mice are treated with

vehicle control (e.g., 5% DMSO, 10% solutol, 85% water) or the compound for 6 or 24 hours past the 3rd dose once tumors reach 400-500 mm^3. Tumors are harvested at given times, bisected and flash frozen. Half of the tumor is analyzed for compound concentration in the tumor or plasma and the other half is analyzed using Western blot to quantify the extent of ER degradation. The compounds of this disclosure are expected to demonstrate dose-dependent ER degradation in MCF-7 tumor model.

Tumor growth inhibition and regression in mice

[0940] To evaluate the ability of compounds of this disclosure to inhibit tumor growth and/or cause tumor growth regression *in vivo*, the MCF-7 human breast carcinoma female athymic nude mouse model is used. Mice are supplemented with 10 μg/mL 17 beta-estradiol in their drinking water 3 days prior to cell implantation and then for the duration of the study. Mice are injected with $1x10^7$ MCF-7 tumor cells in PBS subcutaneously in the flank. Mice are treated with vehicle control (e.g., 5% DMSO, 10% solutol, 85% Water) or the compound once tumors reach 150-200 mm^3, and sacrificed when tumor volume reaches 2000 mm^3 or at the end of the study (whichever occurs first). Tumor sizes and animal weights and caliper measurements of tumors are collected 2-3 times per week. Tumor volume (mm^3) = (length×$width^2$)/2. Tumor growth inhibition is calculated using $^DT/^DC$ TGI (%) = (1-((T_e-T_0)/(C_e-C_0))) * 100, where $^DT/^DC$ is the difference (delta) or change in test vs control TGI; T_e = Test tumor volume endpoint, T_0 = Test tumor volume at start of dosing, C_e = Vehicle control tumor volume endpoint, C_0 = Vehicle control tumor volume at start of dosing. Tumor growth regression is calculated using % Tumor Regression = -(1-(Te/T0))*100) where Te = Test tumor volume (TV) endpoint, Test T0 = TV at start of dosing. The compounds of this disclosure are expected to inhibit tumor growth and induce tumor shrinkage over a range of doses.

INCORPORATION BY REFERENCE

[0941] All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

[0942] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth.

[0943] While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

CLAIMS

WHAT IS CLAIMED IS:

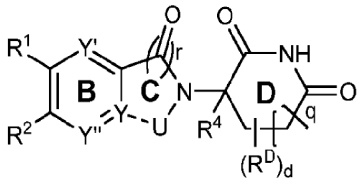
1. A compound of Formula **I**:

T-L-C (I),

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,

wherein:

C is of Formula **I'-1**



(I'-1),

wherein:

R^1 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

R^2 is ***-Cy^2-**, wherein * denotes attachment to **L**;

-Cy^2- is C_{3-12} carbocyclylene or 3- to 12-membered heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted with one or more R^u; or

R^1 and R^2, together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted C_{3-12} carbocycle or 5- to 16-membered heterocycle;

Y" is N or CR^3;

R^3 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, -

$OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; or

R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted 5- to 16-membered heterocycle;

provided that R^1 and R^2, and R^2 and R^3, do not both form Ring A attached to **L**;

Y' is N or $CR^{Y'}$;

$R^{Y'}$ is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

--- denotes an optional covalent bond between Y and U;

i) when the bond between Y and U is absent:

r is 0 or 1;

Y is N or CR^Y;

R^Y is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

U is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

ii) when the bond between Y and U is present:

r is 1;

Y is C;

U is $-CH_2-$, -C(=O)-, $-(C=O)-N(R^U)-*$, or $-N=C(R^U)-*$;

R^U is H or C_{1-6} alkyl optionally substituted with one or more R^u, and * denotes attachment to Ring B;

R^4 is hydrogen, deuterium, C_{1-6} haloalkyl, or C_{1-6} alkyl;

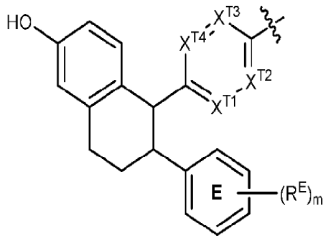
each R^D is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino,

alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

d is an integer from 0 to 4; and

q is an integer from 0 to 2,

T is of Formula **I-2**:



(**I-2**),

wherein:

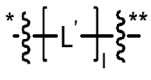
each of X^{T1}, X^{T2}, X^{T3}, and X^{T4} is independently N or CR^T;

each occurrence of R^T is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

each R^E is independently halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

m is an integer selected from 0 to 5;

L is of Formula **I'-3**:



(**I'-3**),

wherein:

* denotes attachment to **T**, and ** denotes attachment to **C**;

each L' is independently C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{3-12} carbocyclylene, 3- to 12-membered heterocyclylene, C_{6-10} arylene, 5- to 10-membered heteroarylene, -C(=O)-, -C(=O)N(R^L)-, -C(=O)O-, -N(R^L)-, -O-, -S-, or -$S(=O)_2$-, wherein the alkylene, heteroalkylene, alkenylene, alkynylene, carbocyclylene, heterocyclylene, arylene, or heteroarylene is optionally substituted with one or more R^u;

each occurrence of R^L is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

l is an integer selected from 0 to 10,

wherein:

each R^u is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2OR^b$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^cS(=O)R^a$, -$NR^cS(=O)_2OR^b$, -$NR^cS(=O)_2NR^cR^d$, -$NR^bC(=O)NR^cR^d$, -$NR^bC(=O)R^a$, -$NR^bC(=O)OR^b$, -$OS(=O)_2R^a$, -$OS(=O)_2OR^b$, -$OS(=O)_2NR^cR^d$, -$OC(=O)R^a$, -$OC(=O)OR^b$, -$OC(=O)NR^cR^d$, -$C(=O)R^a$, -$C(=O)OR^b$, or -$C(=O)NR^cR^d$; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl; or

two R^u, together with the one or more intervening atoms, form C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl;

each R^a is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl;

each R^b is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl; and

each R^c and R^d is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl; or

R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl,

wherein each occurrence of R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z; and

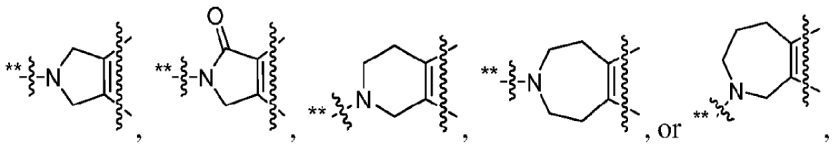
each R^z is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl.

2. The compound of claim 1, wherein

1) when the bond between Y and U is present, U is $-CH_2-$ or -C(=O)-, and r is 1, then

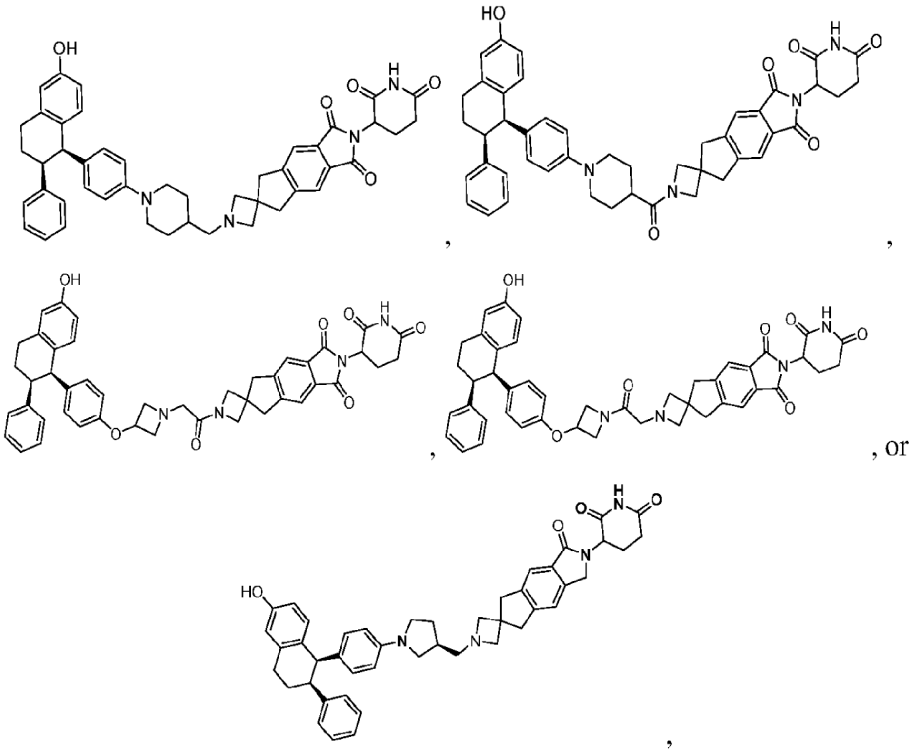
i) either R^1 and R^2, or R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**; and

ii) Ring A is not



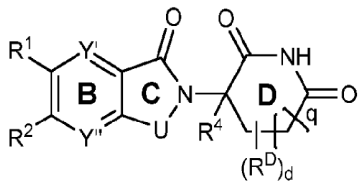
wherein ** denotes attachment to **L**; and

2) the compound is not



or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

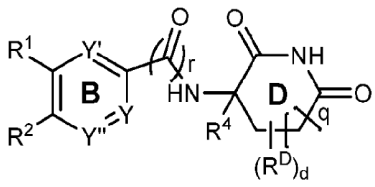
3. The compound of claim 1 or 2, wherein **C** is of Formula **I'-1-i**



(**I'-1-i**).

4. The compound of claim 3, wherein U is $-CH_2-$ or $-C(=O)-$.

5. The compound of claim 1 or 2, wherein **C** is of Formula **I'-1-ii**



(**I'-1-ii**).

6. The compound of claim 5, wherein Y is N.

7. The compound of claim 5, wherein Y is CR^Y, and R^Y is hydrogen, halogen, or C_{1-6} alkoxy.

8. The compound of any one of claims 1-7, wherein R^1 and R^2, together with the intervening carbon atoms, form Ring A attached to **L**, wherein the Ring A is optionally substituted 5- to 16-membered heterocycle.

9. The compound of claim 8, wherein Y" is N.

10. The compound of claim 8, wherein Y" is CR^3, and R^3 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

11. The compound of claim 10, wherein R^3 is hydrogen, halogen, or C_{1-6} alkoxy.

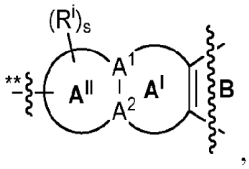
12. The compound of any one of claims 1-7, wherein R^2 and R^3, together with the intervening carbon atoms, form Ring A attached to **L**, wherein the Ring A is optionally substituted 5- to 16-membered heterocycle.

13. The compound of claim 12, wherein R^1 is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

14. The compound of claim 13, wherein R^1 is hydrogen, halogen, or C_{1-6} alkoxy.

15. The compound of any one of claims 1-14, wherein Ring A is optionally substituted 7- to 16-membered fused heterocycle.

16. The compound of any one of claims 1-14, wherein Ring A is



,

wherein:

** denotes attachment to **L**;

Ring A^I and Ring A^{II} are independently C_{4-8} carbocycle or 4- to 8-membered heterocycle; wherein at least one of Ring A^{III} and Ring A^{IV} is 4- to 8-membered heterocycle;

A^1 and A^2 are independently C, CR^{Ax}, or N;

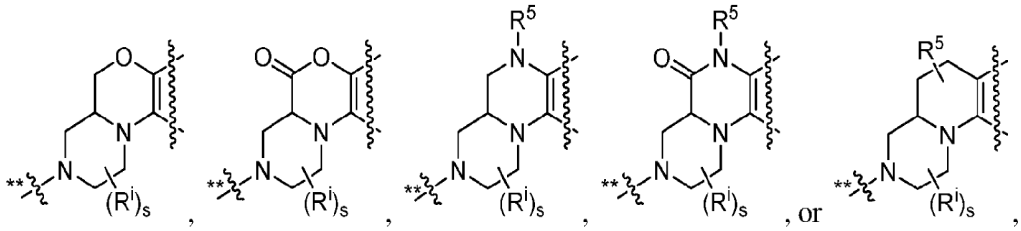
R^{Ax} is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits,

wherein each R^i may independently be present on either Ring A^I or Ring A^{II}.

17. The compound of any one of claims 1-14, wherein Ring A is



, , , , or ,

wherein:

** denotes attachment to **L**;

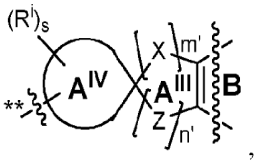
R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits.

18. The compound of any one of claims 1-14, wherein Ring A is optionally substituted 7- to 16-membered spiro heterocycle.

19. The compound of any one of claims 1-14, wherein Ring A is:



,

wherein:

** denotes attachment to **L**;

Ring A^{IV} is C_{3-8} carbocycle or 3- to 8-membered heterocycle;

each X is independently $-C(R^{X1})_2-$, $-NR^{X2}-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$;

each Z is independently $-C(R^{Z1})_2-$, $-NR^{Z2}-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$;

each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, -

$C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; or two geminal R^{X1} or two geminal R^{Z1} together form oxo;

each occurrence of R^{X2} and R^{Z2} is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

m' and n' are independently an integer selected from 0 to 3, wherein m' and n' are not both 0;

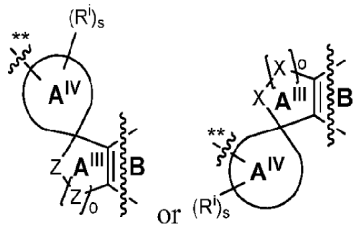
s is an integer selected from 0 to 8, as valency permits, and

each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u,

provided that when none of m' and n' is 0, then Ring A^1 is 4- to 9-membered heterocycle, and each R^i may independently be present on either Ring A^{III} or Ring A^{IV}.

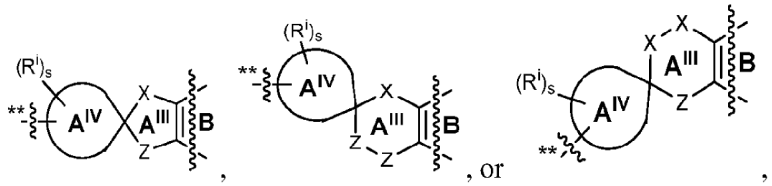
20. The compound of any one of claims 1-14, wherein Ring A is:

1)



wherein o is 0 or 1; or

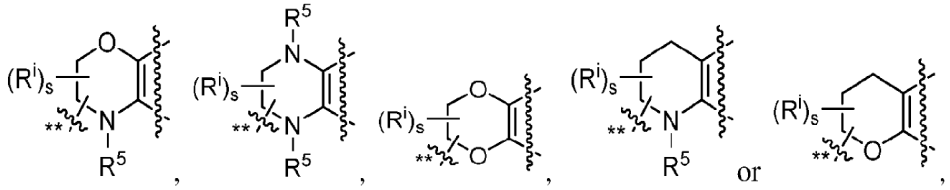
2)



wherein ** denotes attachment to **L**.

21. The compound of any one of claims 1-14, wherein Ring A is optionally substituted 5- to 6-membered heterocycle.

22. The compound of any one of claims 1-14, wherein Ring A is



wherein:

** denotes attachment to **L**;

R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

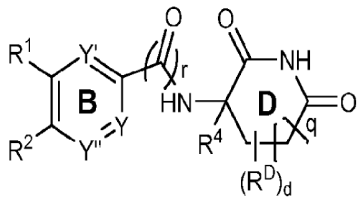
each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits.

23. The compound of any one of claims 16-17, 19-20, and 22, wherein each R^i is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

24. The compound of claim 23, wherein s is 0.

25. The compound of claim 1, wherein **C** is of Formula **I'-1-ii**



(**I'-1-ii**).

26. The compound of claim 25, wherein R^2 is *-Cy^2-, wherein * denotes attachment to **L**.

27. The compound of claim 26, wherein -Cy^2- is C_{5-12} fused carbocyclylene or 5- to 12-membered fused heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted with one or more R^u.

28. The compound of any one of claims 25-27, wherein R^1 is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

29. The compound of claim 28, wherein R^1 is hydrogen, halogen, or C_{1-6} alkoxy.

30. The compound of any one of claims 25-29, wherein Y is N.

31. The compound of any one of claims 25-29, wherein Y is CR^Y, and R^Y is hydrogen, halogen, or C_{1-6} alkoxy.

32. The compound of any one of claims 25-31, wherein Y" is CR^3, and R^3 is hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

33. The compound of claim 32, wherein R^3 is hydrogen, halogen, or C_{1-6} alkoxy.

34. The compound of any one of claims 1-33, wherein Y' is $CR^{Y'}$, and $R^{Y'}$ is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

35. The compound of claim 34, wherein Y' is $CR^{Y'}$, and $R^{Y'}$ is hydrogen, halogen, or C_{1-6} alkoxy.

36. The compound of any one of claims 1-35, wherein R^4 is hydrogen.

37. The compound of any one of claims 1-36, wherein q is 1.

38. The compound of any one of claims 1-37, wherein each of X^{T1}, X^{T2}, X^{T3}, and X^{T4} is CR^T.

39. The compound of claim 38, wherein each of X^{T1}, X^{T2}, X^{T3}, and X^{T4} is CH.

40. The compound of claim 38, wherein X^{T1} is $C(OCH_3)$, X^{T3} is CF, and each of X^{T2} and X^{T4} is CH; X^{T2} is CF, X^{T4} is $C(OCH_3)$, and each of X^{T1} and X^{T3} is CH; one of X^{T1} and X^{T4} is CF or $C(OCH_3)$, the other one of X^{T1} and X^{T4} is CH, and each of X^{T2} and X^{T3} is CH, or X^{T1} is $C(OCH_3)$, X^{T2} is CF, and each of X^{T3} and X^{T4} is CH.

41. The compound of any one of claims 1-37, wherein one of X^{T1}, X^{T2}, X^{T3}, and X^{T4} is N.

42. The compound of claim 41, wherein one of X^{T1} and X^{T4} is N, the other one of X^{T1} and X^{T4} is CH, and each of X^{T2} and X^{T3} is CH; or one of X^{T2} and X^{T3} is N, the other one of X^{T2} and X^{T3} is CH, and each of X^{T1} and X^{T4} is CH.

43. The compound of any one of claims 1-37, wherein two of X^{T1}, X^{T2}, X^{T3}, and X^{T4} are N.

44. The compound of claim 43, wherein each of X^{T1} and X^{T4} is CH, and each of X^{T2} and X^{T3} is N.

45. The compound of any one of claims 38, 41, or 43, wherein each R^T is independently hydrogen, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

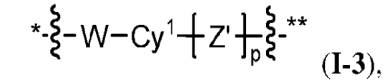
46. The compound of claim 45, wherein each R^T is independently hydrogen or halogen.

47. The compound of any one of claims 38-46, wherein each R^E is independently halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

48. The compound of claim 47, wherein R^E is halogen.

49. The compound of any one of claims 38-48, wherein m is 0.

50. The compound of any one of claims 1-49, wherein **L** is of Formula **I-3**:



(I-3),

wherein:

* denotes attachment to **T** and ** denotes attachment to **C**;

W is absent; or

W is C_{1-3} alkylene, -O-, -NR^W-, or -(C=O)- , wherein the alkylene is optionally substituted by one or more R^u;

Cy^1 is absent; or

Cy^1 is 6-membered heteroarylene, C_6 arylene, C_{3-12} carbocyclylene, or 3- to 12-membered heterocyclylene, wherein the arylene, heteroarylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u;

Z' is absent; or

each Z' is independently C_{1-3} alkylene, -O-, $-NR^W-$, -(C=O)-, C_{3-12} carbocyclylene, or 3- to 12-membered heterocyclylene, wherein the alkylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u;

R^W is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u; and

p is an integer selected from 0 to 8.

51. The compound of claim 50, wherein Cy^1 is C_{3-12} carbocyclylene or 3- to 12-membered heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted by one or more R^u.

52. The compound of claim 50, wherein Cy^1 is 3- to 12-membered heterocyclylene, wherein the heterocyclylene is optionally substituted by one or more R^u.

53. The compound of any one of claims 50-52, wherein W is absent.

54. The compound of any one of claims 50-52, wherein Z' is absent.

55. The compound of any one of claims 50-52, wherein $-[Z']_p-$ is -C(=O)-, C_{1-6} alkylene, *-O-(C_{1-6} alkylene)-, *-(C_{1-6} alkylene)-(C(=O))-O-, *-(C_{1-6} alkylene)-O-, *-C(=O)-(C_{1-6} alkylene)-, *-(C_{1-6} alkylene)-C(=O)-, 3- to 12-membered heterocyclylene, *-C(=O)-(3- to 12-membered heterocyclylene)-, *-(3- to 12-membered heterocyclylene)-C(=O)-, *-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-, *-(C_{1-6} alkylene)-(3- to 12-membered heterocyclylene)-, *-(C_{1-6} alkylene)-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-, *-(C_{1-6} alkylene)-(3- to 12-membered heterocyclylene)-(C(=O))-, *-(C(=O))-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-, *-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-(C(=O))-, *-(C(=O))-(C_{1-6} alkylene)-(3- to 12-membered heterocyclylene)-, *-(C_{1-6} alkylene)-(C(=O))-(3- to 12-membered heterocyclylene)-, or *-(3- to 12-membered heterocyclylene)-(C(=O))-(C_{1-6} alkylene)-, wherein

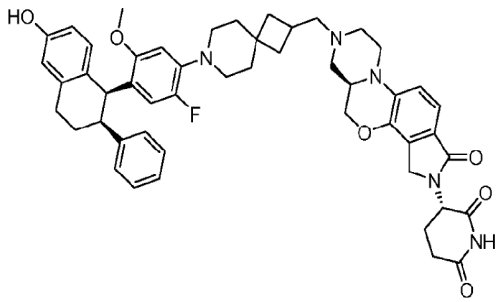
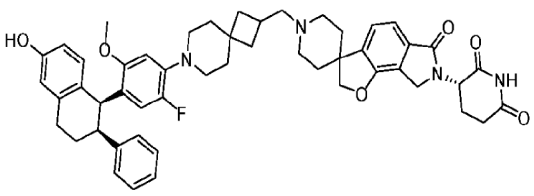
the alkylene or heterocyclylene is optionally substituted by one or more R^u, and *denotes attachment to **C**.

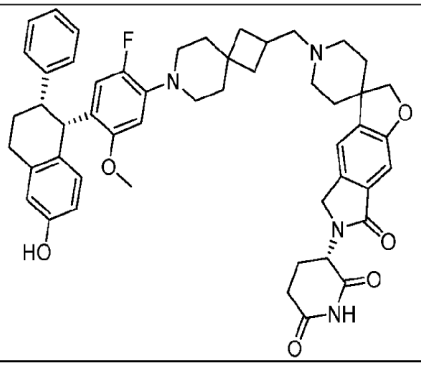
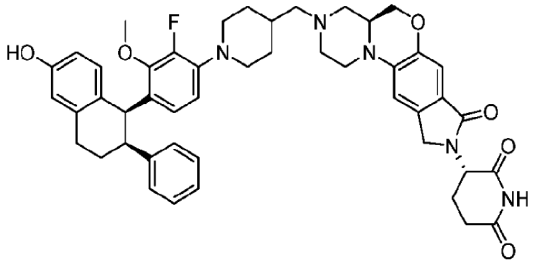
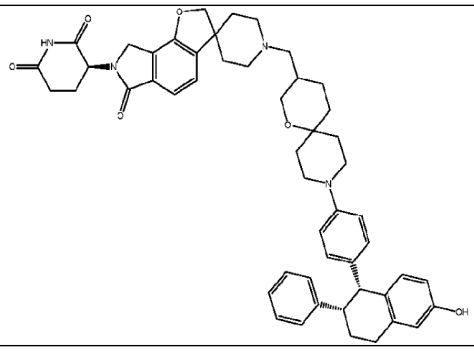
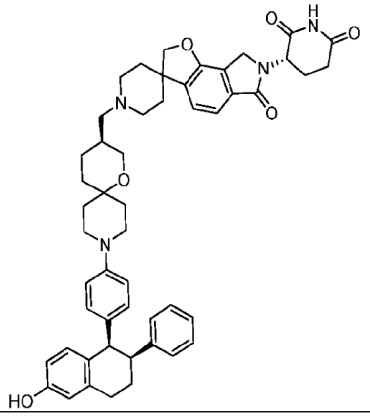
56. The compound of claim 55, wherein $-[Z']_p-$ is -C(=O)-, C_{1-6} alkylene, *-(C_{1-6} alkylene)-(C(=O))-O-, *-C(=O)-(C_{1-6} alkylene)-, *-(C_{1-6} alkylene)-C(=O)-, 3- to 12-membered heterocyclylene, *-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-, *-(C(=O))-(3- to 12-membered heterocyclylene)-(C_{1-6} alkylene)-, *-(C(=O))-(C_{1-6} alkylene)-(3- to 12-membered heterocyclylene)-, *-(C_{1-6} alkylene)-(C(=O))-(3- to 12-membered heterocyclylene)-, wherein the alkylene or heterocyclylene is optionally substituted by one or more R^u, and *denotes attachment to **C**.

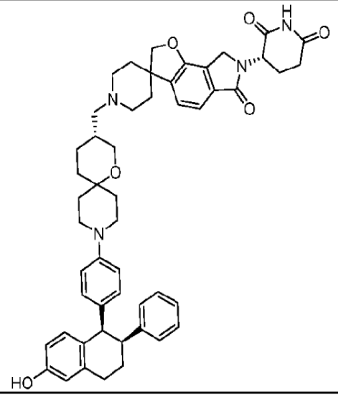
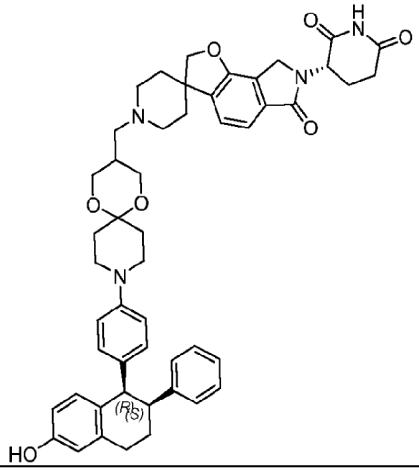
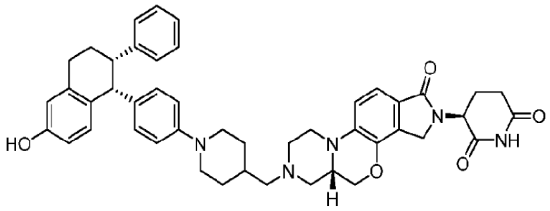
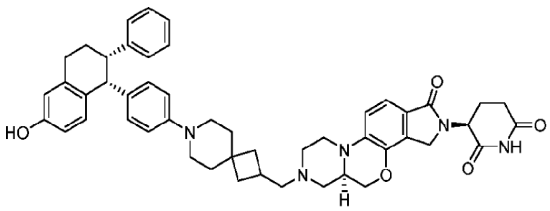
57. A compound selected from the compounds in **Tables 1** and **2**, or a pharmaceutically acceptable salt thereof.

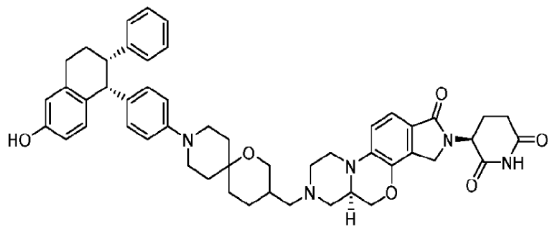
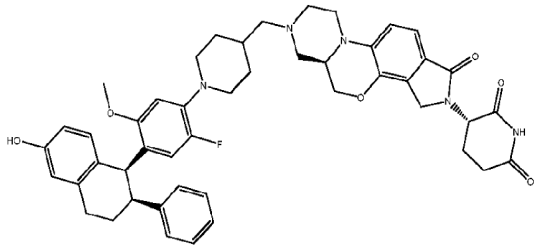
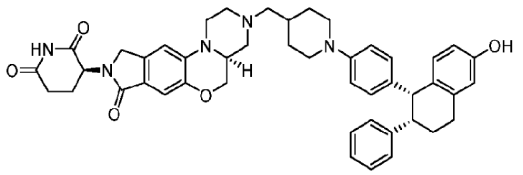
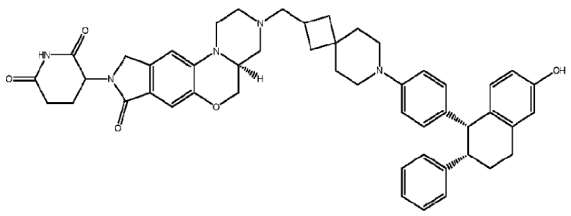
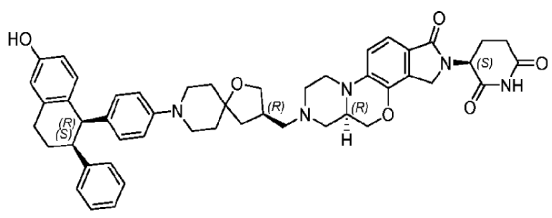
58. A compound selected from **Table X**, or a pharmaceutically acceptable salt thereof.

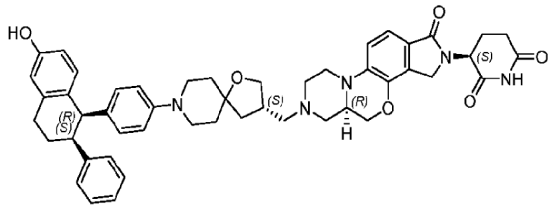
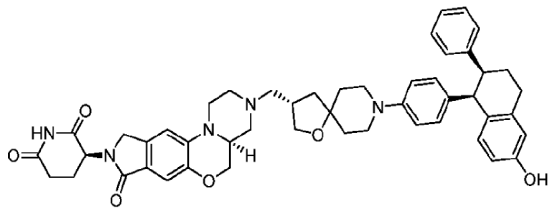
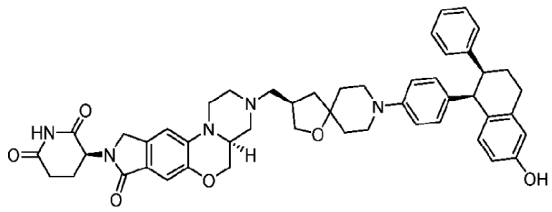
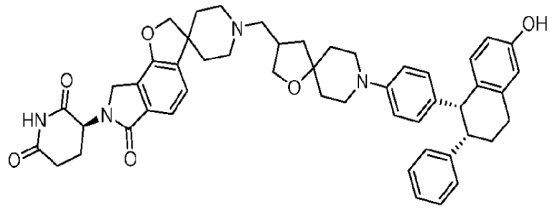
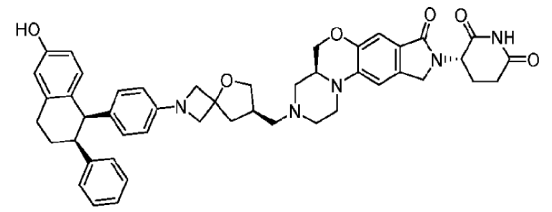
Table X

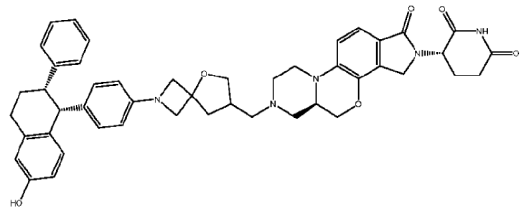
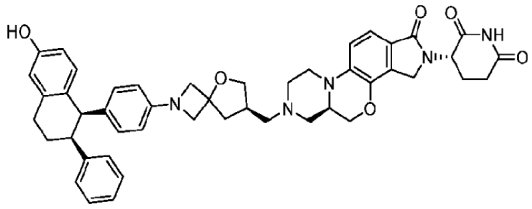
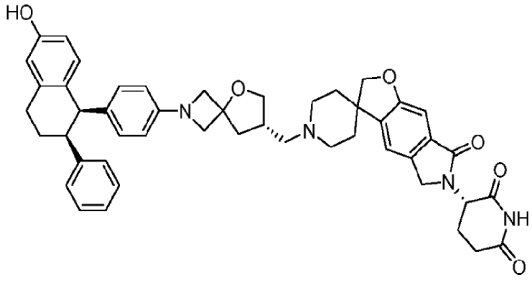
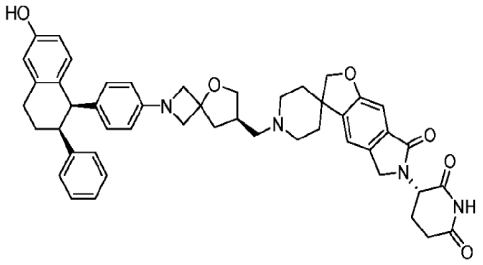
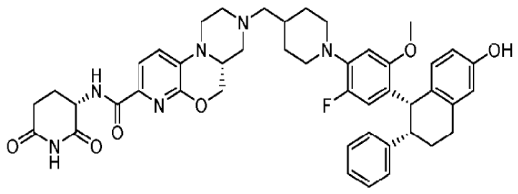
Compound No.	Structure	Chemical Name
A99		(S)-3-((R)-7-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A100		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

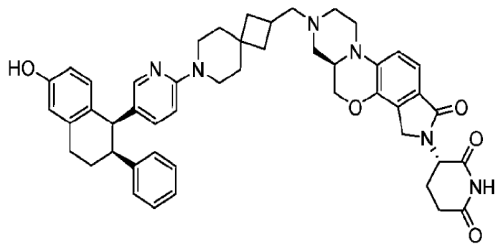
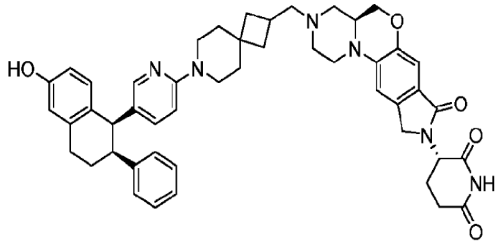
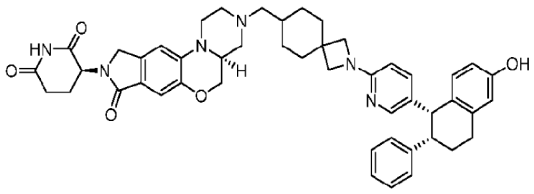
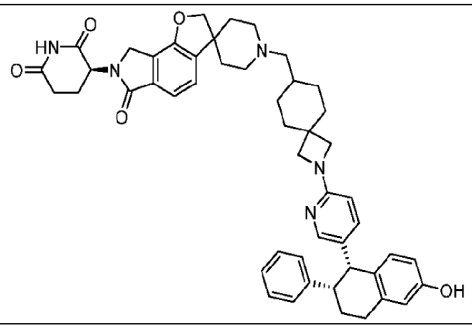
Compound No.	Structure	Chemical Name
A129		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A171		(S)-3-((S)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B366		(3S)-3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B366X		(S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

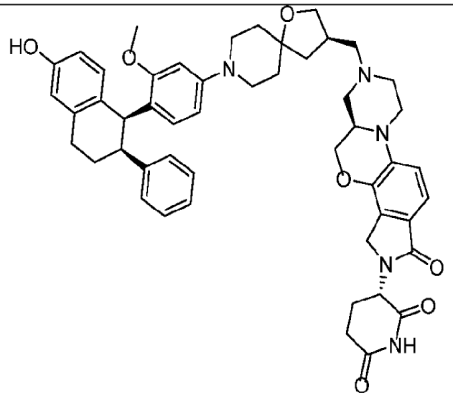
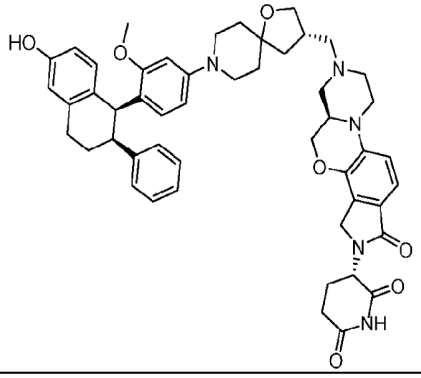
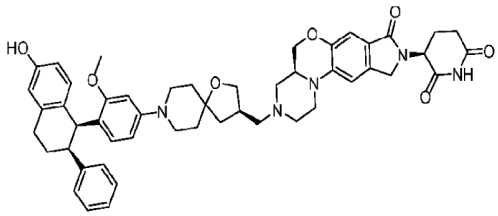
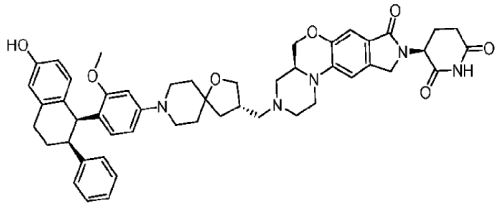
Compound No.	Structure	Chemical Name
B366Y		(S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B337X		(S)-3-(1'-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1,5-dioxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B306X		(S)-3-((S)-7-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B308X		(S)-3-((R)-7-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

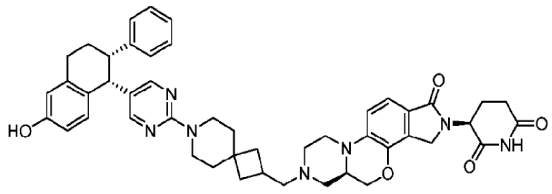
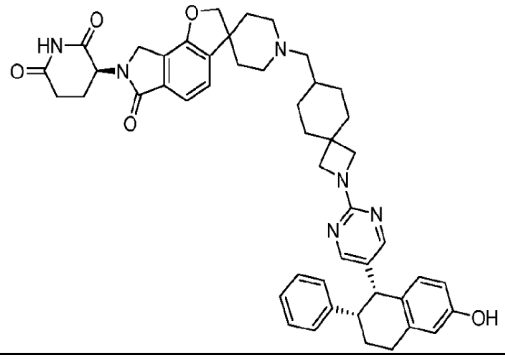
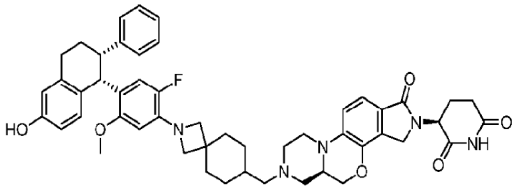
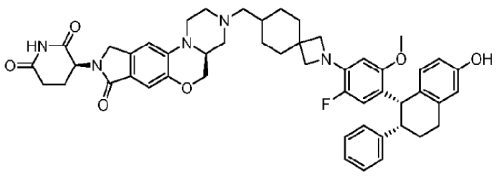
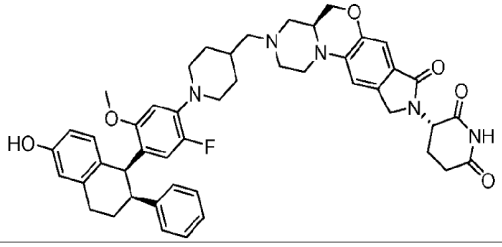
Compound No.	Structure	Chemical Name
B330X		(3S)-3-((5aR)-7-((9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A35		(S)-3-((R)-7-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B135X		(S)-3-((S)-3-((1-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B211		3-((S)-3-((7-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B226X		(S)-3-((R)-7-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

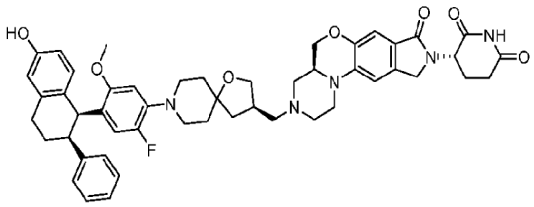
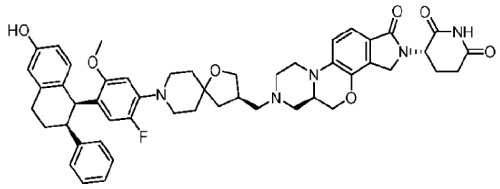
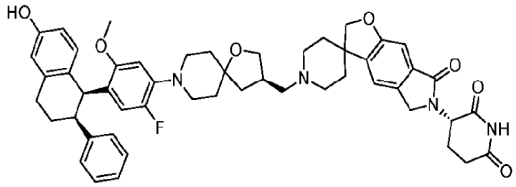
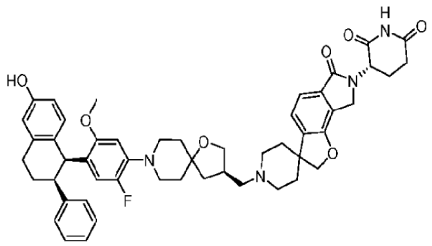
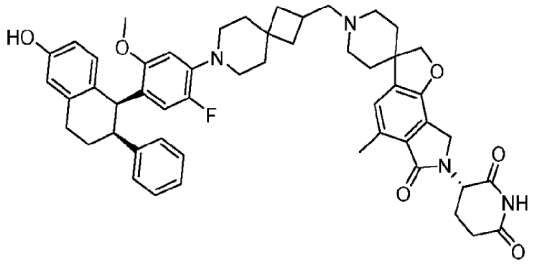
Compound No.	Structure	Chemical Name
B226Y		(S)-3-((R)-7-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B227X		(S)-3-((S)-3-(((S)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B227Y		(S)-3-((S)-3-(((R)-8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
B229X		(3S)-3-(1'-((8-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A73		(S)-3-((S)-3-(((R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2

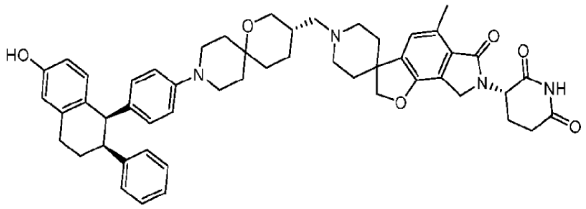
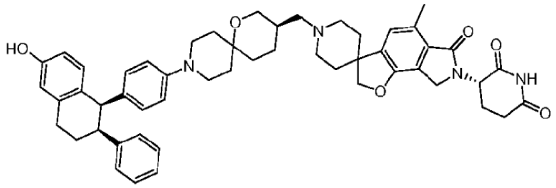
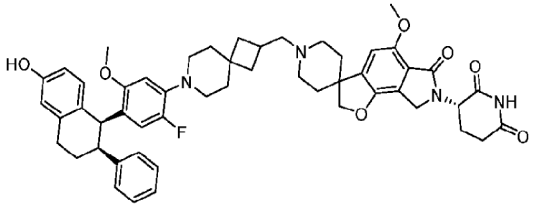
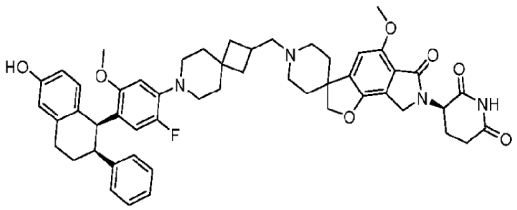
Compound No.	Structure	Chemical Name
		,3-f]isoindol-9-yl)piperidine-2,6-dione
A40		(3S)-3-((5aR)-7-((2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A69		(S)-3-((R)-7-(((R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A76		(S)-3-(1'-(((S)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A77		(S)-3-(1'-(((R)-2-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-5-oxa-2-azaspiro[3.4]octan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A94		(R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-

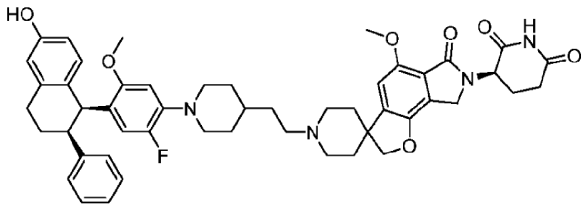
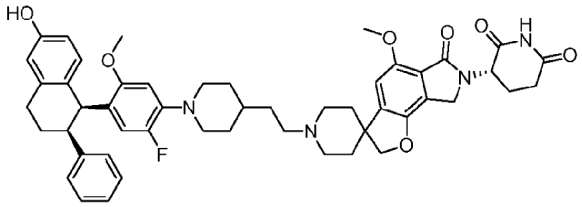
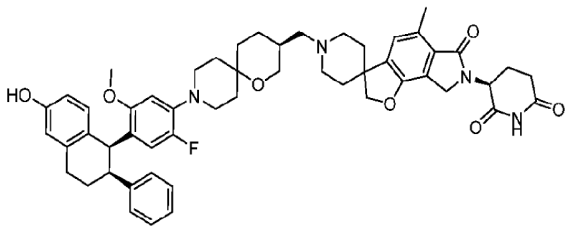
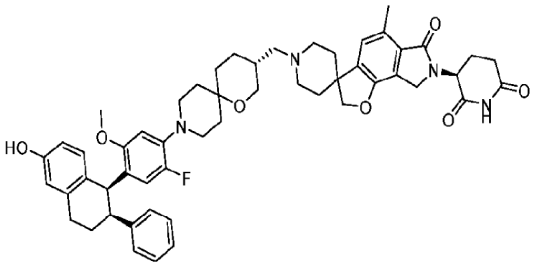
Compound No.	Structure	Chemical Name
		d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A112		(S)-3-((R)-7-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-c]isoindol-2-yl)piperidine-2,6-dione
A121		(S)-3-((S)-3-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A130		(S)-3-((S)-3-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A131		(S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyridin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

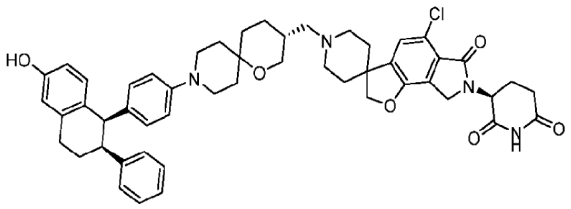
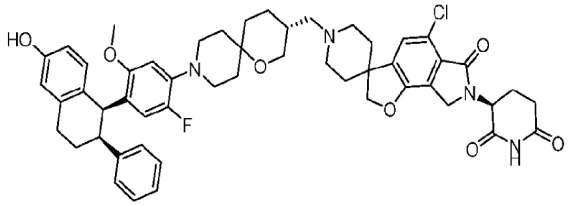
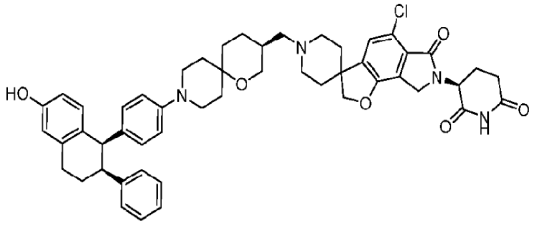
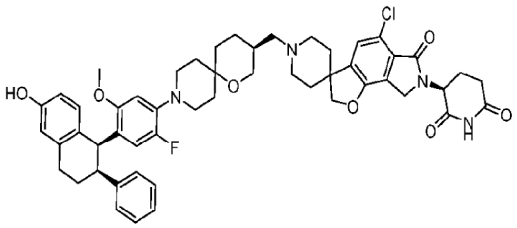
Compound No.	Structure	Chemical Name
A133		(S)-3-((R)-7-(((R)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A134		(S)-3-((R)-7-(((S)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A135		(S)-3-((S)-3-(((R)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A136		(S)-3-((S)-3-(((S)-8-(4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

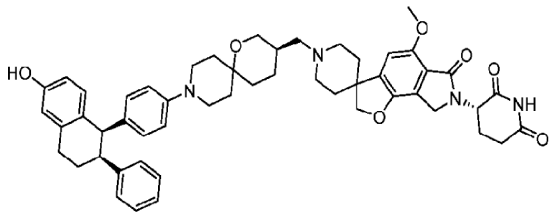
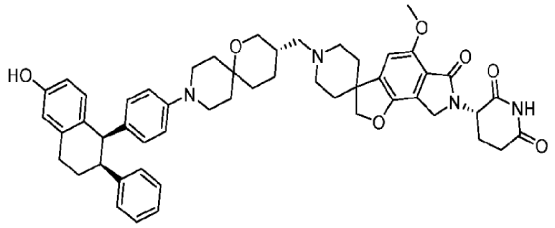
Compound No.	Structure	Chemical Name
A140		(S)-3-((R)-7-((7-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A154		(S)-3-(1'-((2-(5-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)pyrimidin-2-yl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A163		(S)-3-((R)-7-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A164		(S)-3-((S)-3-((2-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A91		(S)-3-((S)-3-((1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2

Compound No.	Structure	Chemical Name
		,3-f]isoindol-9-yl)piperidine-2,6-dione
A173		(S)-3-((S)-3-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A174		(S)-3-((R)-7-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A175		(S)-3-(1'-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A176		(S)-3-(1'-(((R)-8-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A203		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-

Compound No.	Structure	Chemical Name
		3,4'-piperidin]-7-yl)piperidine-2,6-dione
A209		(S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A210		(S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A222		(S)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A223		(R)-3-(1'-((7-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Structure	Chemical Name
A225		(R)-3-(1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A226		(S)-3-(1'-(2-(1-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)piperidin-4-yl)ethyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A227		(S)-3-(1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A230		(S)-3-(1'-(((R)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Structure	Chemical Name
A231		(S)-3-(5-chloro-1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A232		(S)-3-(5-chloro-1'-(((R)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A233		(S)-3-(5-chloro-1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A234		(S)-3-(5-chloro-1'-(((S)-9-(2-fluoro-4-((1S,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)-5-methoxyphenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound No.	Structure	Chemical Name
A235		(S)-3-(1'-(((R)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A236		(S)-3-(1'-(((S)-9-(4-((1R,2S)-6-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenyl)-1-oxa-9-azaspiro[5.5]undecan-3-yl)methyl)-5-methoxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

59. A pharmaceutical composition comprising the compound of any one of claims 1-58, and a pharmaceutically acceptable excipient.

60. A method of degrading an estrogen receptor protein in a patient or biological sample comprising administering to the patient a compound of any one of claims 1-58 or contacting the biological sample with a compound of any one of claims 1-58.

61. Use of a compound of any one of claims 1-58 in the manufacture of a medicament for degrading an estrogen receptor protein in a patient or biological sample.

62. A compound of any one of claims 1-58 for use in degrading an estrogen receptor protein in a patient or biological sample.

63. A method of treating a disease or disorder comprising administering to a patient in need thereof a compound of any one of claims 1-58.

64. Use of a compound of any one of claims 1-58 in the manufacture of a medicament for treating a disease or disorder.

65. A compound of any one of claims 1-58 for use in treating a disease or disorder.

66. The method, use, or compound for use of any one of claims 63-65, wherein the disease or disorder is an estrogen receptor-mediated disease or disorder.

67. The method, use, or compound for use of any one of claims 63-65, wherein the disease or disorder is breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or esophageal cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/027439

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/20 C07D498/14 A61K31/4985 A61K31/438 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2023/143589 A1 (GAN & LEE PHARMACEUTICALS CO LTD [CN]) 3 August 2023 (2023-08-03) claim 1	1-67
X,P	WO 2023/066350 A1 (GLUETACS THERAPEUTICS SHANGHAI CO LTD [CN]) 27 April 2023 (2023-04-27) claim 1	1-67
X,P	WO 2023/023531 A1 (BIOTHERYX INC [US]) 23 February 2023 (2023-02-23) claim 1	1-67
X,P	WO 2022/187588 A1 (UNIV MICHIGAN REGENTS [US]) 9 September 2022 (2022-09-09) claim 1	1-67

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 October 2023	26/10/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bérillon, Laurent

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/132652 A1 (ARVINAS OPERATIONS INC [US]) 23 June 2022 (2022-06-23)	1-4, 8-14, 34-56, 59-67
Y	claim 1 specific compounds of claim 12	1-67
X	WO 2021/143822 A1 (JIANGSU HENGRUI MEDICINE CO [CN] ET AL.) 22 July 2021 (2021-07-22)	1-4, 8-14, 34-56, 59-67
Y	claim 1 examples 10 and 12	1-67
X	WO 2021/041348 A1 (ARVINAS OPERATIONS INC [US]) 4 March 2021 (2021-03-04)	1-4, 8-14, 34-56, 59-67
Y	claim 1 specific compounds of claim 10	1-67
X	WO 2019/199816 A1 (ARVINAS OPERATIONS INC [US]) 17 October 2019 (2019-10-17)	1-4, 8-14, 34-56, 59-67
Y	claim 1 examples 1-31	1-67
X	WO 2018/144649 A1 (ARVINAS INC [US]) 9 August 2018 (2018-08-09)	1-4, 8-14, 34-56, 59-67
Y	claim 1 protac 90 to 92 on page 475	1-67
X	WO 2018/102725 A1 (ARVINAS INC [US]) 7 June 2018 (2018-06-07)	1-4, 8-14, 34-56, 59-67
Y	claim 1 specific compounds of figure 5	1-67
Y	WO 2021/041664 A1 (UNIV MICHIGAN REGENTS [US]) 4 March 2021 (2021-03-04) claim 1	1-67
Y	WO 2020/006265 A1 (DANA FARBER CANCER INST INC [US]) 2 January 2020 (2020-01-02) claim 1	1-67

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International application No
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Information on patent family members

International application No
PCT/US2023/027439

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		IL 266842 A	31-07-2019
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		US 2022388978 A1	08-12-2022
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