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(54) **Title:** CHROMAN DERIVATIVES AS ESTROGEN RECEPTOR DEGRADERS

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

# CHROMAN DERIVATIVES AS ESTROGEN RECEPTOR DEGRADERS

## RELATED APPLICATIONS

**[0001]** This application claims the benefit of and priority to U.S. Provisional Application No. 63/388,297, filed July 12, 2022; and U.S. Provisional Application No. 63/408,601, filed September 21, 2022; 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

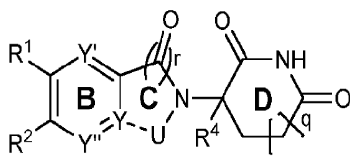
[0005] In certain aspects, the present disclosure provides compounds of Formula **I**:

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

and pharmaceutically acceptable salts, solvates, or stereoisomers thereof,

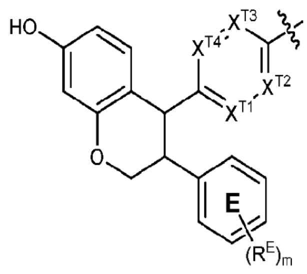
wherein:

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



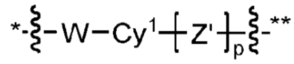
(**I-1**),

**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.

**[0015]** 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

**[0016]** 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 invention 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**

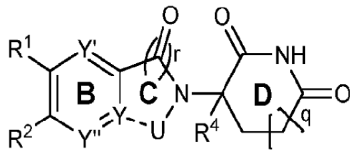
**[0017]** In certain aspects, the present disclosure provides compounds of Formula **I**:

**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 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 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;

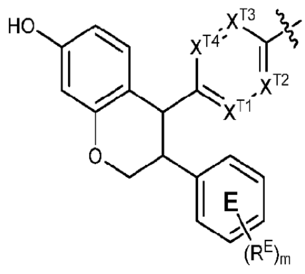
U is $-CH_2-$, -C(=O)-, -(C=O)-N($R^U$)-*, or -N=C($R^U$)-*;

$R^U$ 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 $R^E$ 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**:

$$*\text{-}W-Cy^1-[Z']_p\text{-}** \quad \textbf{(I-3)},$$

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, $C_{3-12}$ membered 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)-, $C_{3-12}$ membered 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 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.

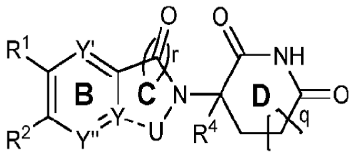
**[0018]** In certain aspects, the present disclosure provides compounds of Formula **I**:

**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

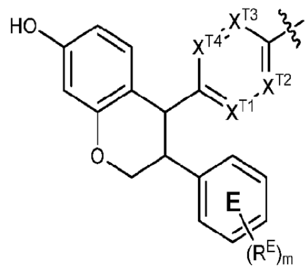
U is $-CH_2-$, -C(=O)-, $-(C=O)-N(R^U)-*$, $-N=C(R^U)-*$ when the bond between Y and U is present;

$R^U$ 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**),

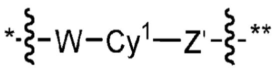
wherein:

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

each $R^{E}$ 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, $-SR^{b}$, $-S(=O)R^{a}$, $-S(=O)_2R^{a}$, $-S(=O)_2OR^{b}$, $-S(=O)_2NR^{c}R^{d}$, $-NR^{c}S(=O)_2R^{a}$, $-NR^{c}S(=O)R^{a}$, $-NR^{c}S(=O)_2OR^{b}$, $-NR^{c}S(=O)_2NR^{c}R^{d}$, $-NR^{b}C(=O)NR^{c}R^{d}$, $-NR^{b}C(=O)R^{a}$, $-NR^{b}C(=O)OR^{b}$, $-OS(=O)_2R^{a}$, $-OS(=O)_2OR^{b}$, $-OS(=O)_2NR^{c}R^{d}$, $-OC(=O)R^{a}$, $-OC(=O)OR^{b}$, $-OC(=O)NR^{c}R^{d}$, $-C(=O)R^{a}$, $-C(=O)OR^{b}$, or $-C(=O)NR^{c}R^{d}$, 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:

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, $C_{3-12}$ membered 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)$_2NR^cR^d$, -$NR^c$S(=O)$_2R^a$, -$NR^c$S(=O)$R^a$, -$NR^c$S(=O)$_2OR^b$, -$NR^c$S(=O)$_2NR^cR^d$, -$NR^b$C(=O)$NR^cR^d$, -$NR^b$C(=O)$R^a$, -$NR^b$C(=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

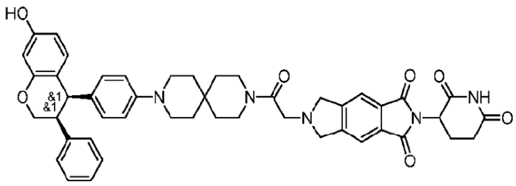
$R^c$ and $R^d$, together with the nitrogen atom to which they are attached, form 3- to 10-membered heterocyclyl,

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, the compound is not



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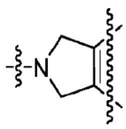
**[0021]** In certain embodiments, when the bond between Y and U is present, U is -$CH_2$- or -C(=O)-, and r is 1, then Ring A is not



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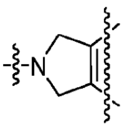
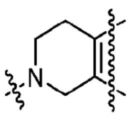
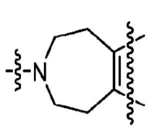
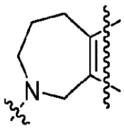
**[0022]** In certain embodiments, when the bond between Y and U is present, U is -$CH_2$- or -C(=O)-, and r is 1, then Ring A is not



, 

, 

, or 

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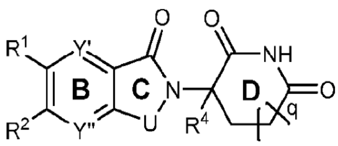
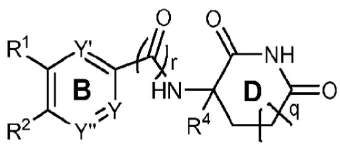
**[0023]** In certain embodiments, **C** is of Formula **I-1-i**



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

**[0024]** 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.

**[0025]** In certain embodiments, **C** is of Formula **I-1-ii**

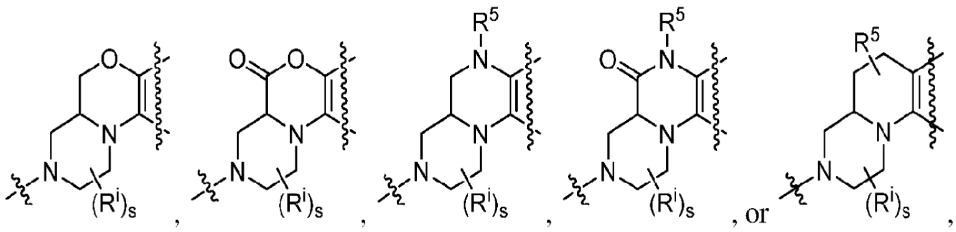


(**I-1-ii**).

**[0026]** In certain embodiments, $R^1$ 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.

**[0027]** In certain embodiments, Ring A is optionally substituted 7- to 16-membered fused heterocycle.

**[0028]** In certain embodiments, Ring A is



wherein:

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

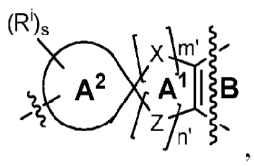
each $R^i$ is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylamino, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{6-10}$ aryl, 5- to 10-membered heteroaryl, $C_{3-12}$ carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$,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

**[0029]** In certain embodiments, $R^5$ is hydrogen. In certain embodiments, $R^5$ is $C_{1-6}$ alkyl.

**[0030]** In certain embodiments, Ring A is optionally substituted 7- to 16-membered spiro heterocycle.

**[0031]** In certain embodiments, Ring A is:



wherein:

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.

**[0032]** In certain embodiments, when none of m' and n' is 0, then Ring $A^1$ is 4- to 9-membered heterocycle.

**[0033]** In certain embodiments, Ring $A^2$ is $C_{3-8}$ carbocycle. In certain embodiments, Ring $A^2$ is 3- to 8-membered heterocycle.

**[0034]** In certain embodiments, each X is independently $-C(R^{X1})_2-$, $-NR^{X2}-$, or -O-.

**[0035]** In certain embodiments, each Z is independently $-C(R^{Z1})_2-$, $-NR^{Z2}-$, or -O-.

**[0036]** In certain embodiments, m' and n' are independently an integer selected from 0-2, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0-2, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0 and 1, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0 and 1, wherein m' and n' are not both 0.

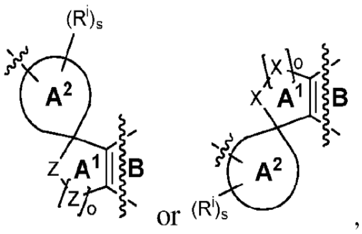
**[0037]** In certain embodiments, each occurrence of $R^{X1}$ and $R^{Z1}$ is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylamino, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{6-10}$ aryl, 5- to 10-membered heteroaryl, $C_{3-6}$ carbocyclyl, 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 $R^u$;

**[0038]** In certain embodiments, two geminal $R^{X1}$ or two geminal $R^{Z1}$ together form oxo.

**[0039]** 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 $R^u$.

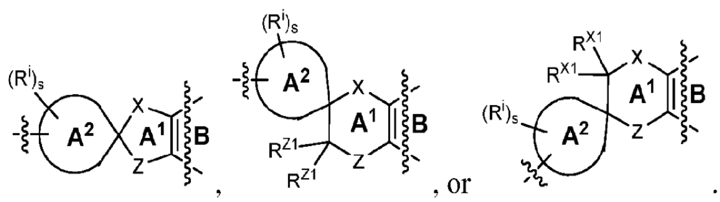
**[0040]** In certain embodiments, Ring A is:

1)



wherein o is 0 or 1; or

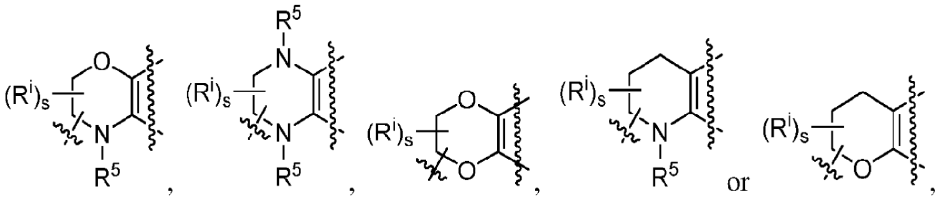
2)



**[0041]** In certain embodiments, o is 0. In certain embodiments, o is 1.

**[0042]** In certain embodiments, Ring A is optionally substituted 5- to 6-membered heterocycle.

**[0043]** In certain embodiments, Ring A is



wherein:

$R^5$ 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.

**[0044]** In certain embodiments, $R^5$ is hydrogen. In certain embodiments, $R^5$ is $C_{1-6}$ alkyl.

**[0045]** In certain embodiments, Y" is N.

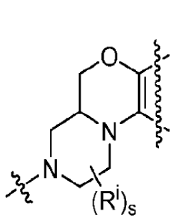
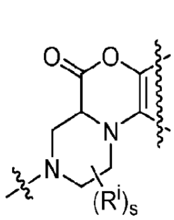
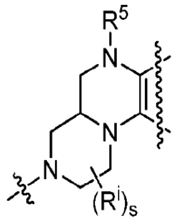
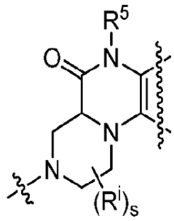
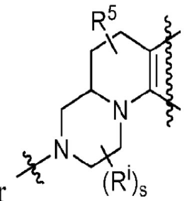
**[0046]** In certain embodiments, Y" is $CR^3$, and $R^3$ is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylamino, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{6-10}$ aryl, 5- to 10-membered heteroaryl, $C_{3-12}$ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more $R^u$.

**[0047]** In certain embodiments, $R^3$ is hydrogen, halogen, or $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

**[0048]** In certain embodiments, $R^2$ 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.

**[0049]** In certain embodiments, Ring A is optionally substituted 7- to 16-membered fused heterocycle.

**[0050]** In certain embodiments, Ring A is

, , , , or ,

wherein:

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

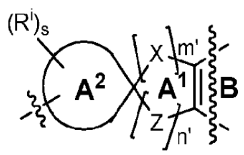
each $R^i$ is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylamino, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{6-10}$ aryl, 5- to 10-membered heteroaryl, $C_{3-12}$ carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$,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

**[0051]** In certain embodiments, $R^5$ is hydrogen. In certain embodiments, $R^5$ is $C_{1-6}$ alkyl.

**[0052]** In certain embodiments, Ring A is optionally substituted 7- to 16-membered spiro heterocycle.

**[0053]** In certain embodiments, Ring A is:

,

wherein:

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.

**[0054]** In certain embodiments, when none of m' and n' is 0, then Ring $A^1$ is 4- to 9-membered heterocycle.

**[0055]** In certain embodiments, Ring $A^2$ is $C_{3-8}$ carbocycle. In certain embodiments, Ring $A^2$ is 3- to 8-membered heterocycle.

**[0056]** In certain embodiments, each X is independently $-C(R^{X1})_2-$, $-NR^{X2}-$, or -O-.

**[0057]** In certain embodiments, each Z is independently $-C(R^{Z1})_2-$, $-NR^{Z2}-$, or -O-.

**[0058]** In certain embodiments, m' and n' are independently an integer selected from 0-2, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0-2, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0 and 1, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0 and 1, wherein m' and n' are not both 0.

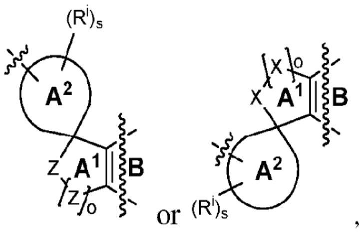
**[0059]** In certain embodiments, each occurrence of $R^{X1}$ and $R^{Z1}$ is independently hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylamino, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{6-10}$ aryl, 5- to 10-membered heteroaryl, $C_{3-6}$ carbocyclyl, 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 $R^u$;

**[0060]** In certain embodiments, two geminal $R^{X1}$ or two geminal $R^{Z1}$ together form oxo.

**[0061]** 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 $R^u$.

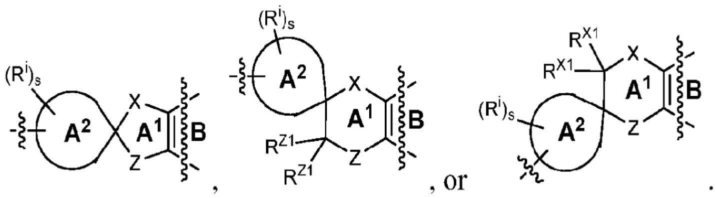
**[0062]** In certain embodiments, Ring A is:

1)



wherein o is 0 or 1; or

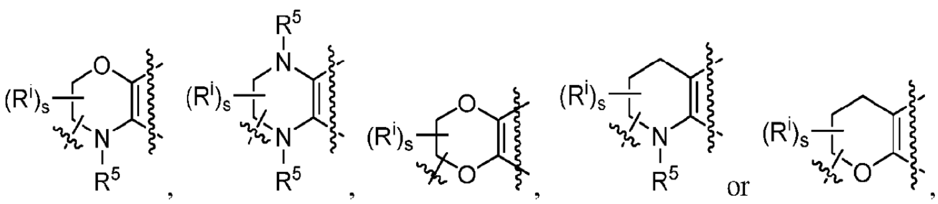
2)



**[0063]** In certain embodiments, o is 0. In certain embodiments, o is 1.

**[0064]** In certain embodiments, Ring A is optionally substituted 5- to 6-membered heterocycle.

**[0065]** In certain embodiments, Ring A is



wherein:

$R^5$ 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.

**[0066]** In certain embodiments, $R^5$ is hydrogen. In certain embodiments, $R^5$ is $C_{1-6}$ alkyl.

**[0067]** 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, $C_{6-10}$ 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 $R^u$.

**[0068]** In certain embodiments, wherein $R^1$ is hydrogen, halogen, or $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

**[0069]** 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, $C_{6-10}$ 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 $R^u$.

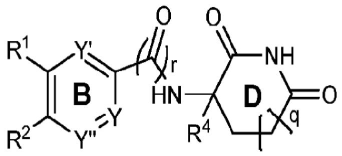
**[0070]** In certain embodiments, s is 0. In certain embodiments, s is 1. In certain embodiments, s is 2. In certain embodiments, s is 3. In certain embodiments, s is 4. In certain embodiments, s is 5. In certain embodiments, s is 6. In certain embodiments, s is 7. In certain embodiments, s is 8.

**[0071]** In certain embodiments, Ring A is optionally substituted with one or more $R^u$.

**[0072]** In certain embodiments, $R^u$ is $R^5$. In certain embodiments, $R^u$ is $R^i$. 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 $R^{Z2}$.

**[0073]** In certain embodiments, Ring A 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, $C_{6-10}$ 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.

**[0074]** In certain embodiments, **C** is of Formula **I-1-ii**




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

**[0075]** In certain embodiments, $R^2$ is ***-**$Cy^2$-, wherein * denotes attachment to **L**.

**[0076]** In certain embodiments, *-$Cy^2$- is 3-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 4-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 5-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 6-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 7-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 8-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 9-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 10-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 11-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 12-membered heterocyclylene. In certain embodiments, the above *-$Cy^2$- is optionally substituted with one or more $R^u$.

**[0077]** In certain embodiments, *-$Cy^2$- is 3- to 12-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 3- to 11-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 3- to 10-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 3- to 9-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 3- to 8-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 3- to 7-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 3- to 6-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 3- to 5-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 3- to 4-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 4- to 12-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 4-

to 11-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 4- to 10-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 4- to 9-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 4- to 8-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 4- to 7-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 4- to 6-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 4- to 5-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 5- to 12-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 5- to 11-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 5- to 10-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 5- to 9-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 5- to 8-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 5- to 7-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 5- to 6-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 6- to 12-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 6- to 11-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 6- to 10-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 6- to 9-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 6- to 8-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 6- to 7-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 8- to 12-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 8- to 11-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 8- to 10-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 8- to 9-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 9- to 12-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 9- to 11-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 9- to 10-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 10- to 12-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 10- to 11-membered heterocyclylene. In certain embodiments, *-$Cy^2$- is 11- to 12-membered heterocyclylene. In certain embodiments, the above *-$Cy^2$- is optionally substituted with one or more $R^u$.

**[0078]** In certain embodiments, *-$Cy^2$- is heterocyclylene comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, *-$Cy^2$- is heterocyclylene comprising 2 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, *-$Cy^2$- is heterocyclylene comprising 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, *-$Cy^2$- is heterocyclylene comprising 4 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the above *-$Cy^2$- is optionally substituted with one or more $R^u$.

**[0079]** In certain embodiments, *-$Cy^2$- is heterocyclylene comprising 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, *-$Cy^2$- is heterocyclylene comprising 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, *-$Cy^2$- is heterocyclylene comprising 1 to 2 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, *-$Cy^2$- is heterocyclylene comprising 2 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, *-$Cy^2$- is heterocyclylene comprising 2 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, *-$Cy^2$- is heterocyclylene comprising 3 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the above *-$Cy^2$- is optionally substituted with one or more $R^u$.

**[0080]** In certain embodiments, *-$Cy^2$- is $C_3$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_4$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_5$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_6$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_7$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_8$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_9$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{10}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{11}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{12}$ carbocyclylene. In certain embodiments, the above *-$Cy^2$- is optionally substituted with one or more $R^u$.

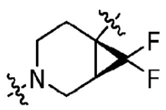
**[0081]** In certain embodiments, *-$Cy^2$- is $C_{3-12}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{3-11}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{3-10}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{3-9}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{3-8}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{3-7}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{3-6}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{3-5}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{3-4}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{4-12}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{4-11}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{4-10}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{4-9}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{4-8}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{4-7}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{4-6}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{4-5}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{5-12}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{5-11}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{5-10}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{5-9}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{5-8}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{5-7}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{5-6}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{6-12}$

carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{6-11}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{6-10}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{6-9}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{6-8}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{6-7}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{7-12}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{7-11}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{7-10}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{7-9}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{7-8}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{8-12}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{8-11}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{8-10}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{8-9}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{9-12}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{9-11}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{9-10}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{10-12}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{10-11}$ carbocyclylene. In certain embodiments, *-$Cy^2$- is $C_{11-12}$ carbocyclylene. In certain embodiments, the above *-$Cy^2$- is optionally substituted with one or more $R^u$.

**[0082]** 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 Ru.

**[0083]** 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 Ru.

**[0084]** In certain embodiments, *-$Cy^2$- is




.

**[0085]** 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, $C_{6-10}$ 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 $R^u$.

**[0086]** In certain embodiments, $R^1$ is hydrogen, halogen, or $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

**[0087]** In certain embodiments, Y" is N.

**[0088]** In certain embodiments, Y" is $CR^3$.

**[0089]** 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, $C_{6-10}$ 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 $R^u$.

**[0090]** In certain embodiments, $R^3$ is hydrogen, halogen, or $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

**[0091]** In certain embodiments, Y is N.

**[0092]** In certain embodiments, Y is $CR^Y$.

**[0093]** 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, $C_{6-10}$ 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 $R^u$.

**[0094]** In certain embodiments, $R^Y$ is hydrogen, halogen, or $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.In certain embodiments, r is 0. In certain embodiments, r is 1.

**[0095]** In certain embodiments, $R^4$ is hydrogen. In certain embodiments, $R^4$ is deuterium. In certain embodiments, $R^4$ is $C_{1-6}$ haloalkyl. In certain embodiments, $R^4$ is $C_{1-6}$ alkyl.

**[0096]** In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2.

**[0097]** In certain embodiments, each of $X^{T1}$, $X^{T2}$, $X^{T3}$, and $X^{T4}$ is $CR^T$.

**[0098]** 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 $C(OCH_3)$, 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.

**[0099]** In certain embodiments, one of $X^{T1}$, $X^{T2}$, $X^{T3}$, and $X^{T4}$ is N.

**[0100]** 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.

**[0101]** In certain embodiments, two of $X^{T1}$, $X^{T2}$, $X^{T3}$, and $X^{T4}$ are N.

**[0102]** In certain embodiments, each of $X^{T1}$ and $X^{T4}$ is CH, and each of $X^{T2}$ and $X^{T3}$ is N.

**[0103]** 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 $R^u$.

**[0104]** In certain embodiments, each $R^T$ is independently hydrogen, $C_{1-6}$ alkoxy, or halogen.

**[0105]** 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 $R^u$.

**[0106]** In certain embodiments, $R^E$ is $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

**[0107]** 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.

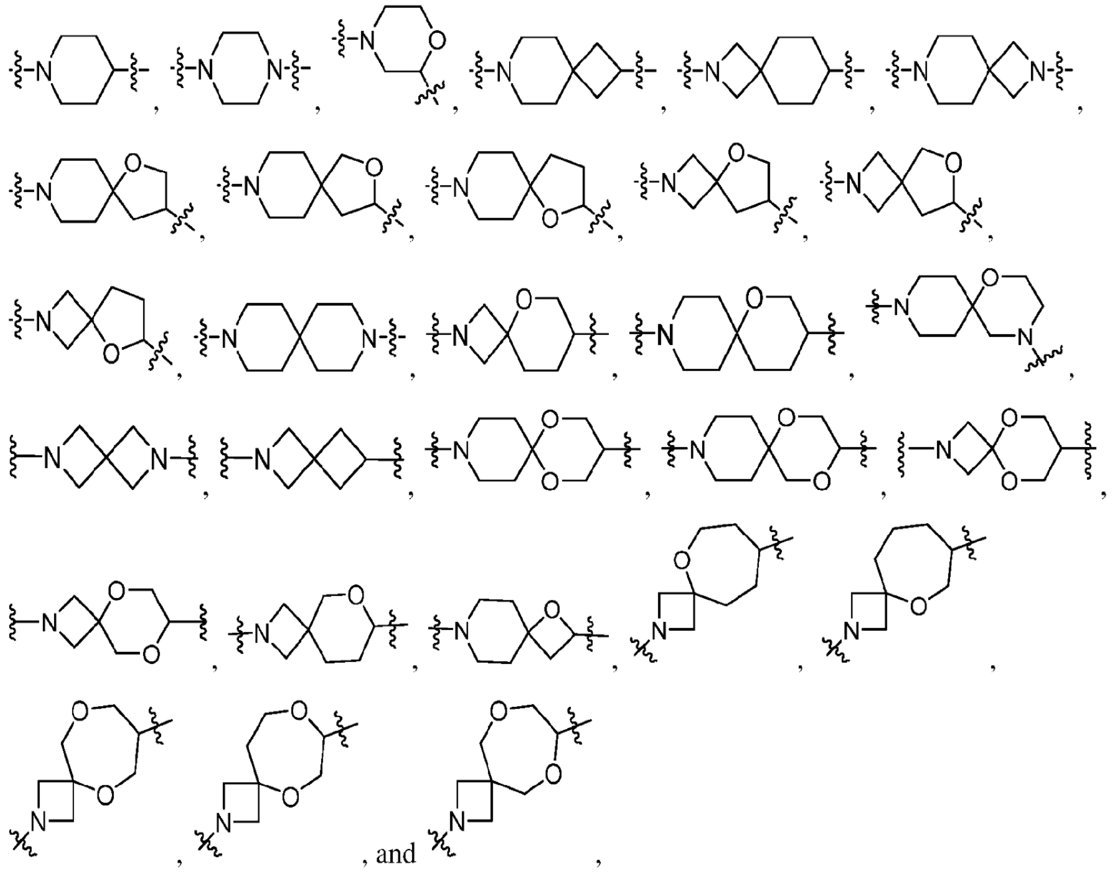
**[0108]** In certain embodiments, $Cy^1$ is $C_{3-10}$ carbocyclylene or 3- to 12-membered heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted by one or more $R^u$. In certain embodiments, $Cy^1$ is 6-membered heteroarylene or $C_6$ arylene, wherein the heterocyclylene is optionally substituted by one or more $R^u$.

**[0109]** In certain embodiments, $Cy^1$ is 3- to 12-membered heterocyclylene, wherein the heterocyclylene is optionally substituted by one or more $R^u$.

**[0110]** 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 $R^u$.

**[0111]** In certain embodiments, $Cy^1$ is 3- to 12-membered heterocyclylene selected from:



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

**[0112]** In certain embodiments, W is absent.

**[0113]** In certain embodiments, Z' is absent.

**[0114]** In certain embodiments, Z' is -C(=O)-, $C_{1-6}$ alkylene, *-O-($C_{1-6}$ alkylene)-, *-($C_{1-6}$ 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**.

**[0115]** In certain embodiments, Z' is $C_{1-6}$ alkylene, *-C(=O)-($C_{1-6}$ alkylene)-, *-($C_{1-6}$ alkylene)-C(=O)-,*-C(=O)-(3- to 12-membered heterocyclylene)-, or *-(3- to 12-membered heterocyclylene)-($C_{1-6}$ alkylene)-, wherein the alkylene or heterocyclylene is optionally substituted by one or more $R^u$, and *denotes attachment to **C**.

**[0116]** In certain embodiments, the compound is selected from the compounds in Tables 1-3, or a pharmaceutically acceptable salt thereof.

**[0117]** In certain embodiments, the compound is selected from the compounds in Tables 1-3.

**[0118]** In certain embodiments, the compound is selected from the compounds in Table 1, or a pharmaceutically acceptable salt thereof.

**[0119]** In certain embodiments, the compound is selected from the compounds in Table 1.

**[0120]** In certain embodiments, the compound is selected from the compounds in Table 2, or a pharmaceutically acceptable salt thereof.

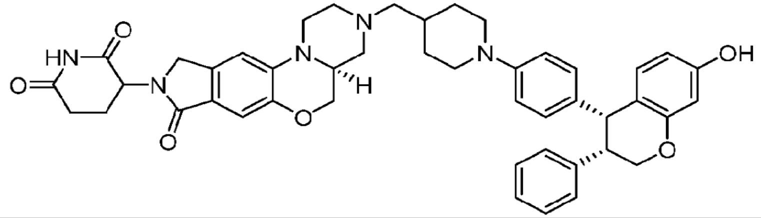
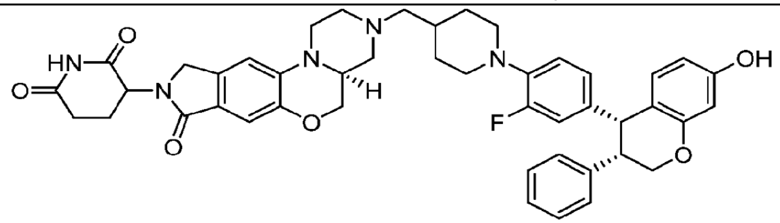
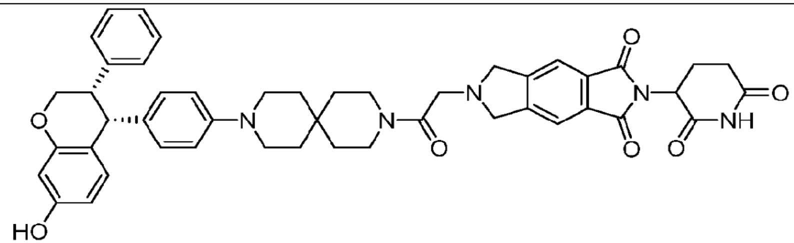
**[0121]** In certain embodiments, the compound is selected from the compounds in Table 2.

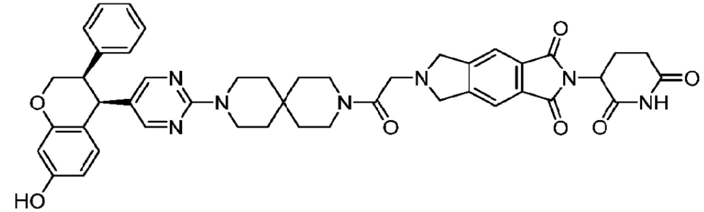
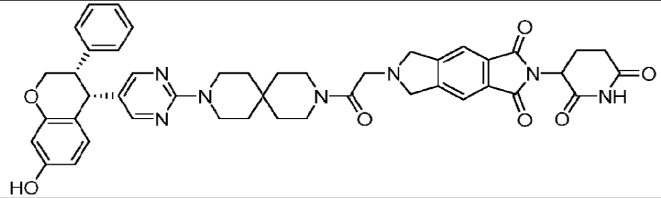
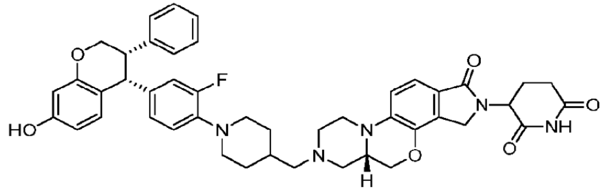
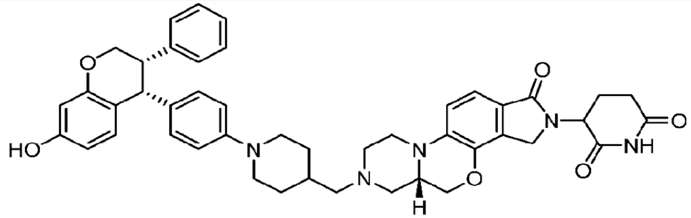
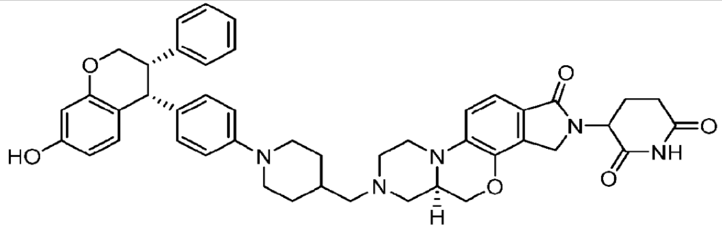
**[0122]** In certain embodiments, the compound is selected from the compounds in Table 3, or a pharmaceutically acceptable salt thereof.

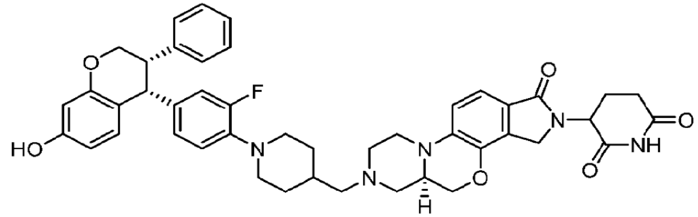
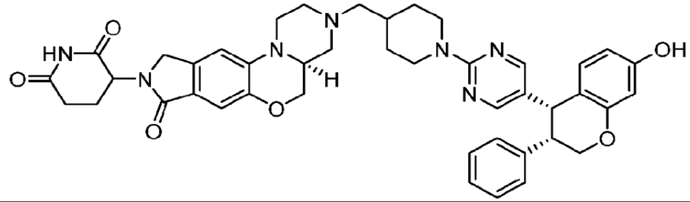
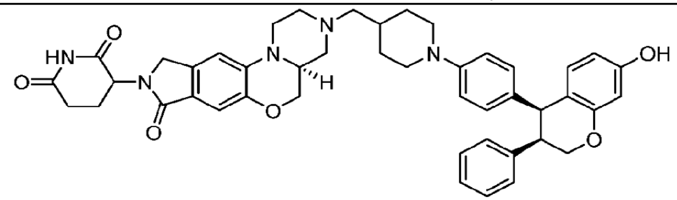
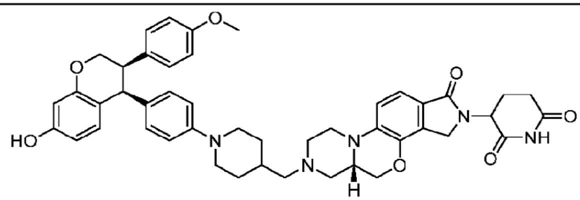
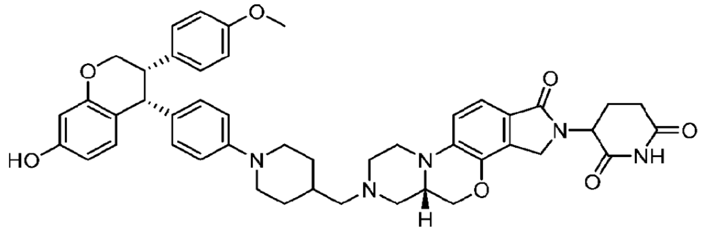
**[0123]** In certain embodiments, the compound is selected from the compounds in Table 3.

**Table 1**.

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

| Compound No. | Structure | Compound Name |
|---|---|---|
| **A1*** |  | 3-((S)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A2*** |  | 3-((S)-3-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A3*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |

| | | |
|---|---|---|
| **A4*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
| **A5*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A6*** |  | 3-((S)-7-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A7*** |  | 3-((S)-7-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A8*** |  | 3-((R)-7-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |

| | | |
|---|---|---|
| **A9*** |  | 3-((R)-7-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A10*** |  | 3-((S)-3-((1-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)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 |
| **A11*** |  | 3-((S)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
| **A12*** |  | 3-((S)-7-((1-(4-((3R,4S)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-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 |
| **A13*** |  | 3-((S)-7-((1-(4-((3S,4R)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-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 |

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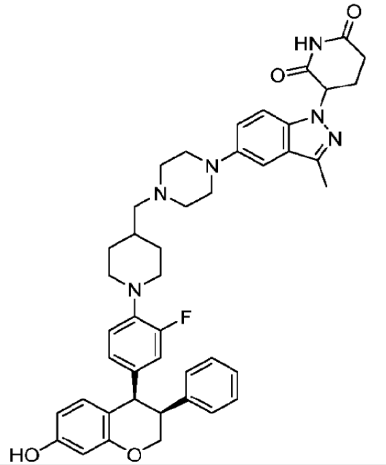
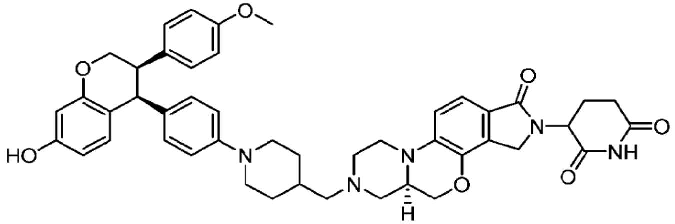
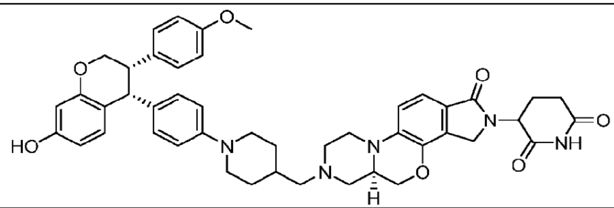
| **A14*** |  | 3-(5-(4-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-1H-indazol-1-yl)piperidine-2,6-dione |
| **A15*** |  | 3-((R)-7-((1-(4-((3R,4S)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A16*** |  | 3-((R)-7-((1-(4-((3S,4R)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-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 |

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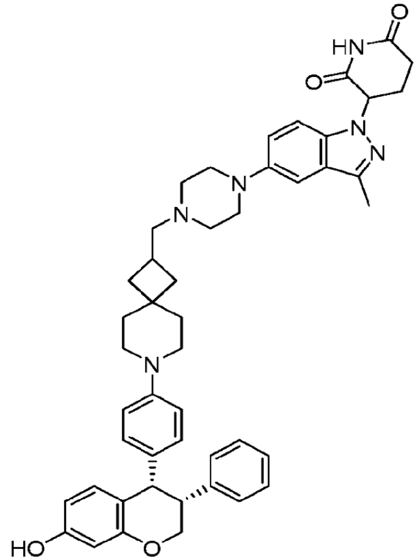
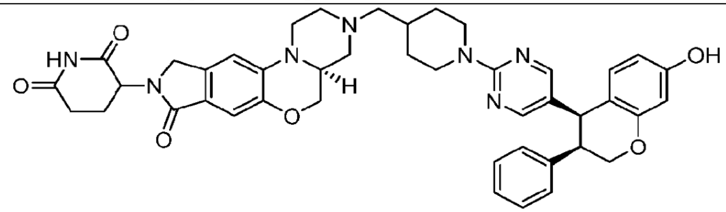
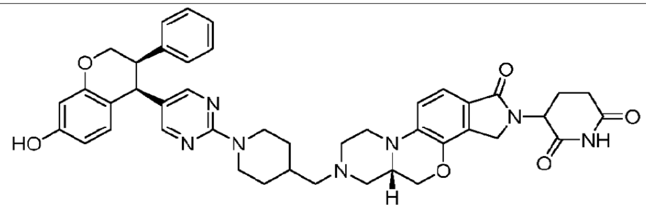
| **A17*** |  | 3-(5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-3-methyl-1H-indazol-1-yl)piperidine-2,6-dione |
| **A18*** |  | 3-((S)-3-((1-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione |
| **A19*** |  | 3-((S)-7-((1-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)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 |

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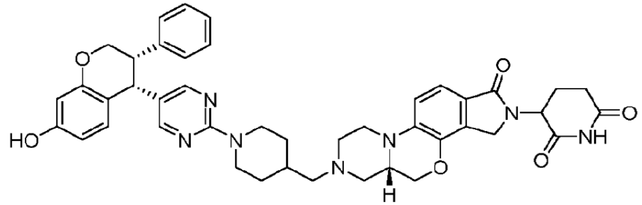
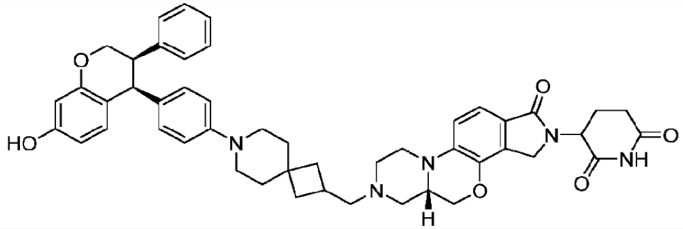
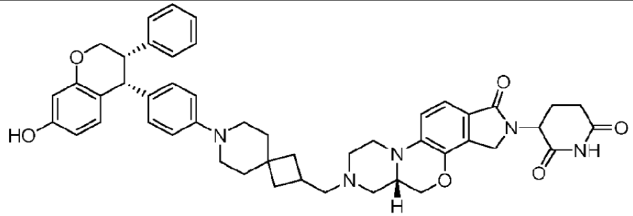
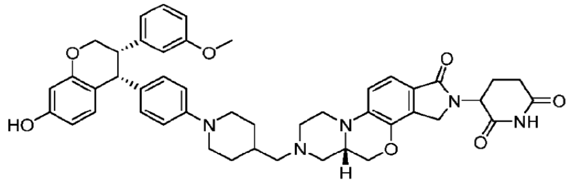
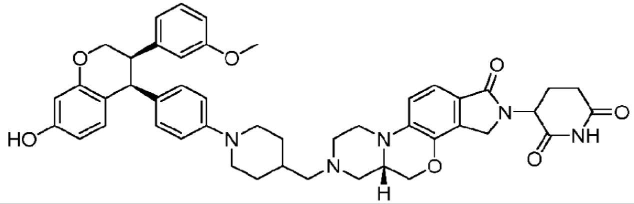
| **A20*** |  | 3-((S)-7-((1-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A21*** |  | 3-((S)-7-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A22*** |  | 3-((S)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A23*** |  | 3-((S)-7-((1-(4-((3S,4R)-7-hydroxy-3-(3-methoxyphenyl)chroman-4-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 |
| **A24*** |  | 3-((S)-7-((1-(4-((3R,4S)-7-hydroxy-3-(3-methoxyphenyl)chroman-4-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 |

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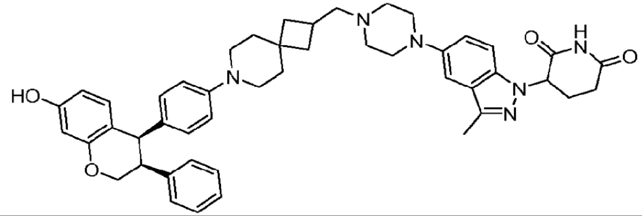
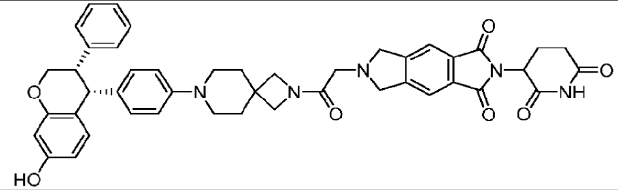
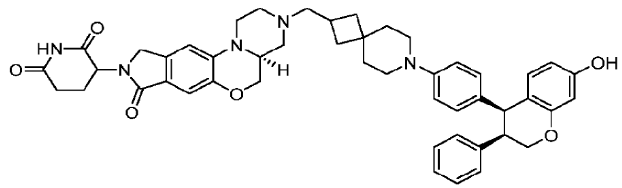
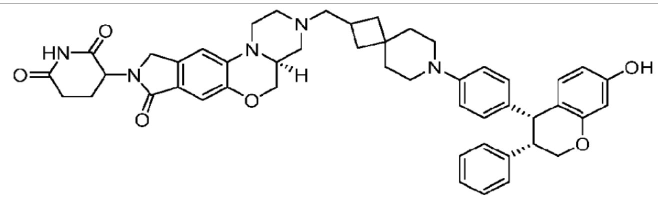
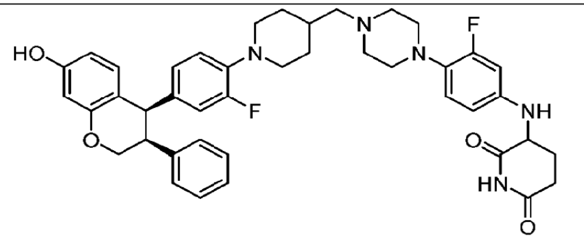
| **A25*** |  | 3-(5-(4-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-3-methyl-1H-indazol-1-yl)piperidine-2,6-dione |
| **A26*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |
| **A27*** |  | 3-((S)-3-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
| **A28*** |  | 3-((S)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A29*** |  | 3-((3-fluoro-4-(4-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenyl)amino)piperidine-2,6-dione |

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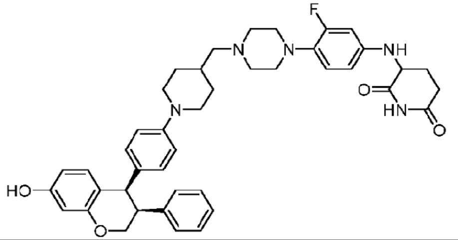
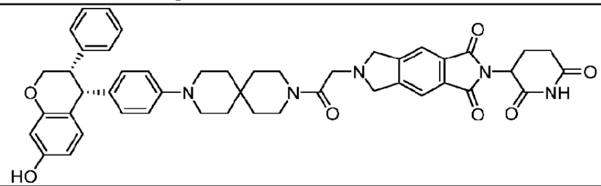
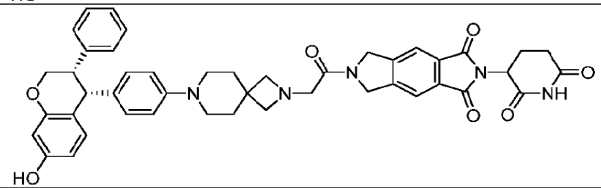
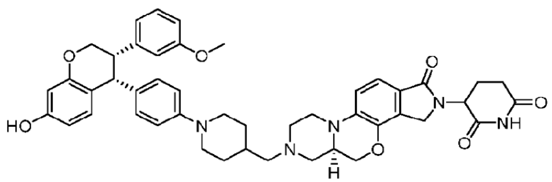
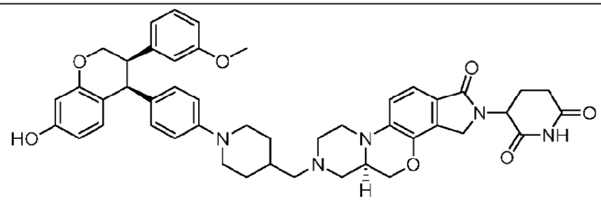
| **A30*** |  | 3-((3-fluoro-4-(4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenyl)amino)piperidine-2,6-dione |
| **A31*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |
| **A32*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |
| **A33*** |  | 3-((R)-7-((1-(4-((3S,4R)-7-hydroxy-3-(3-methoxyphenyl)chroman-4-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 |
| **A34*** |  | 3-((R)-7-((1-(4-((3R,4S)-7-hydroxy-3-(3-methoxyphenyl)chroman-4-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 |

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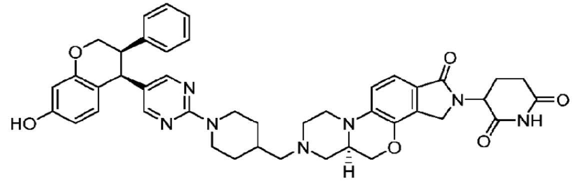
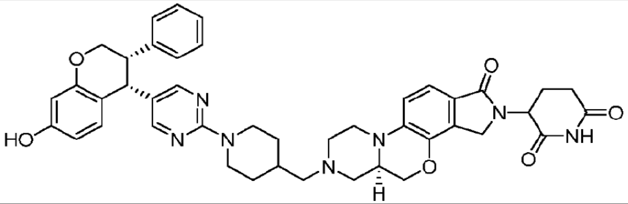
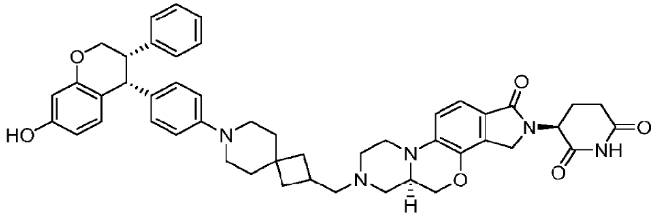
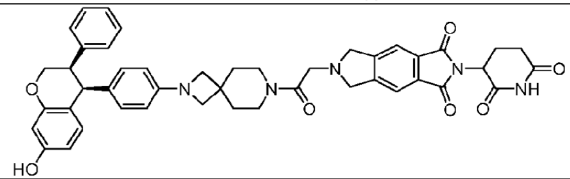
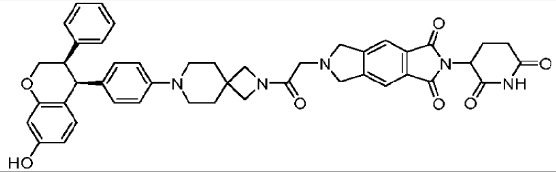
| **A35*** |  | 3-((R)-7-((1-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A36*** |  | 3-((R)-7-((1-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A37*** |  | (S)-3-((R)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A38*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |
| **A39*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |

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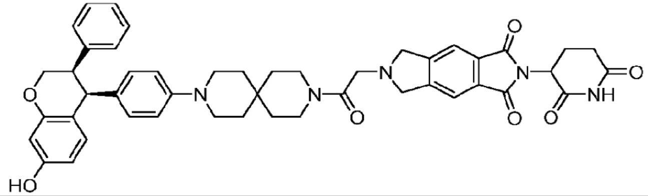
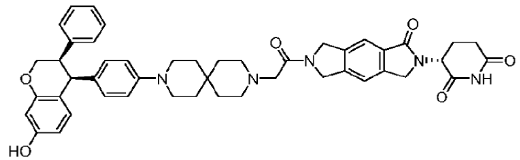
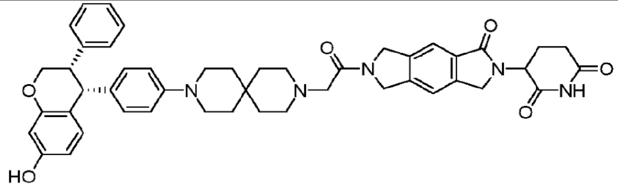
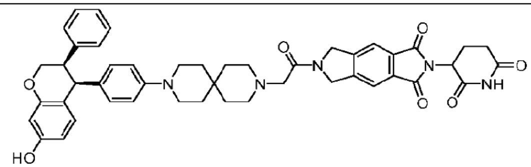
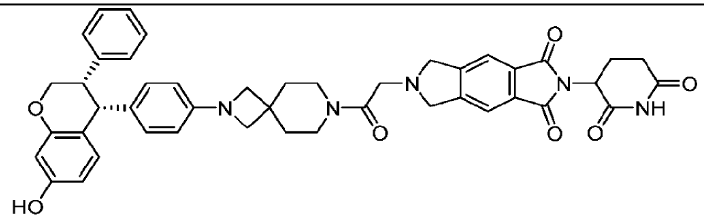
| **A40*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |
| **A41*** |  | (R)-3-(6-(2-(9-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione |
| **A42*** |  | 3-(6-(2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A43*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |
| **A44*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |

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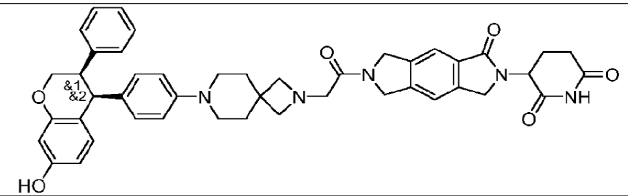
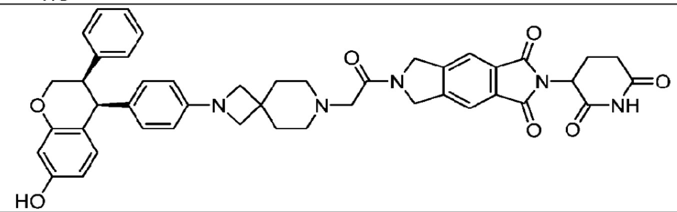
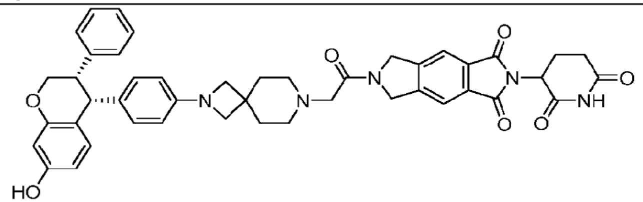
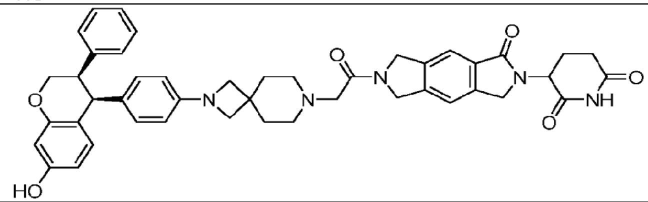
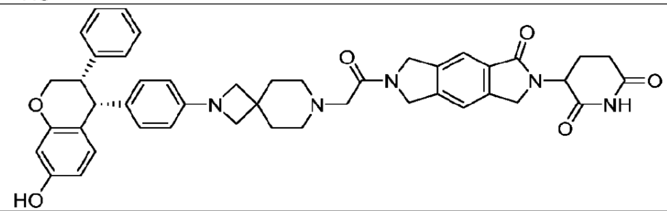
|---|---|---|
| **A45*** |  | 3-(6-(2-(7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione |
| **A46*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |
| **A47*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |
| **A48*** |  | 3-(6-(2-(2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione |
| **A49*** |  | 3-(6-(2-(2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione |

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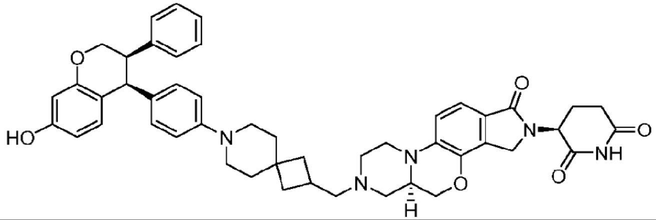
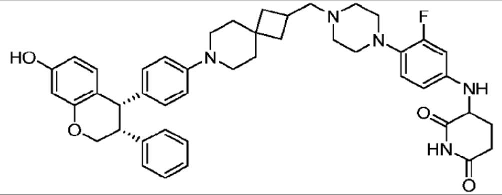
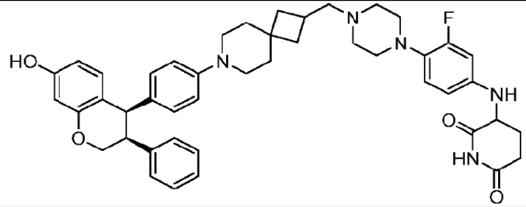
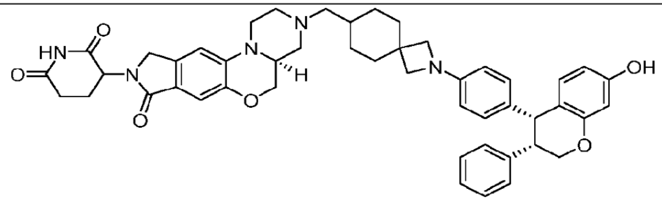
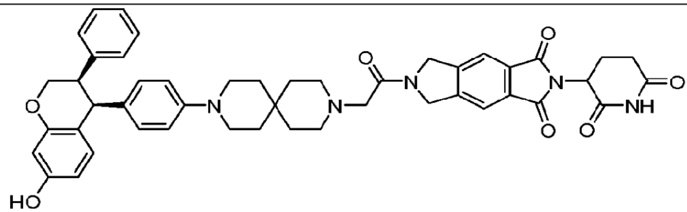
| **A50*** |  | (S)-3-((R)-7-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A51*** |  | 3-((3-fluoro-4-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)phenyl)amino)piperidine-2,6-dione |
| **A52*** |  | 3-((3-fluoro-4-(4-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)phenyl)amino)piperidine-2,6-dione |
| **A53*** |  | 3-((S)-3-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A54*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione formate |

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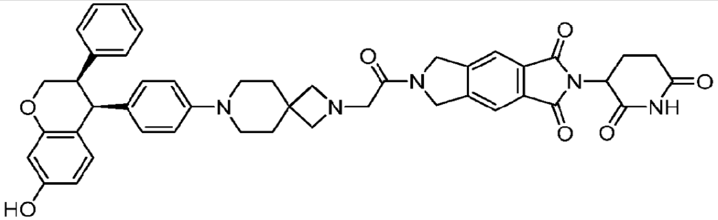
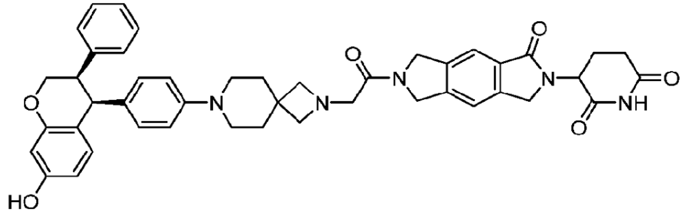
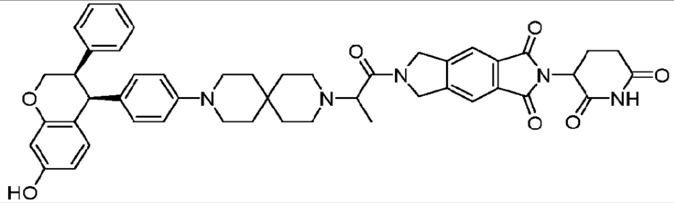
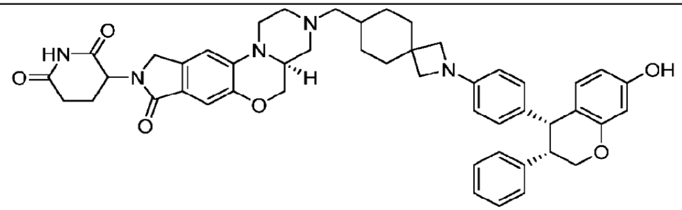
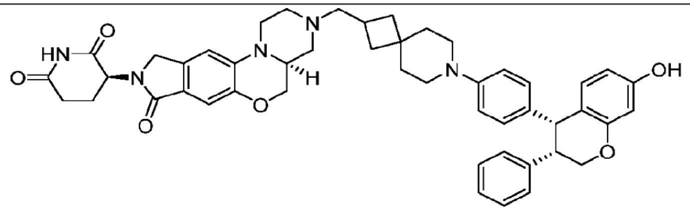
| **A55*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione formate |
| **A56*** |  | 3-(6-(2-(7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione formate |
| **A57*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)propanoyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |
| **A58*** |  | 3-((S)-3-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A59*** |  | (S)-3-((S)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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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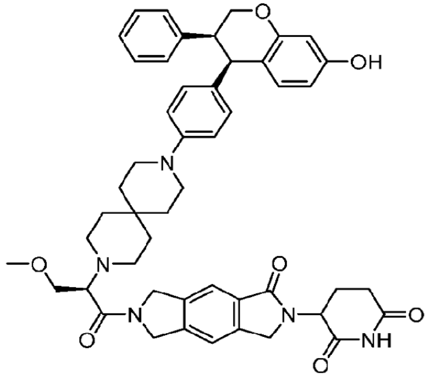
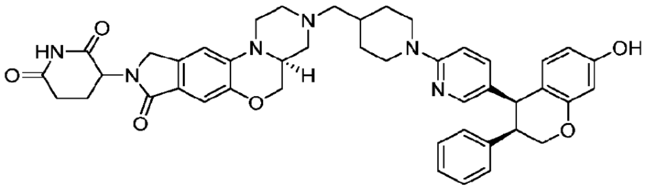
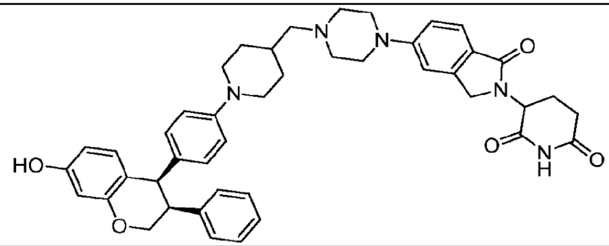
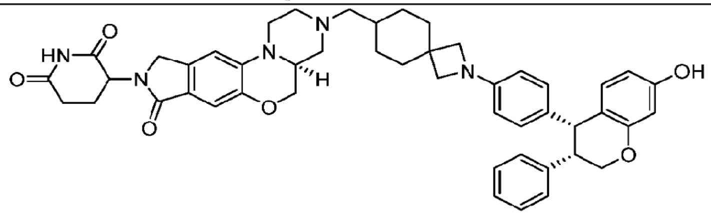
| **A60*** |  | 3-(6-((R)-2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-3-methoxypropanoyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione |
| **A61*** |  | 3-((S)-3-((1-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione |
| **A62*** |  | 3-(5-(4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione |
| **A63*** |  | 3-((S)-3-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |

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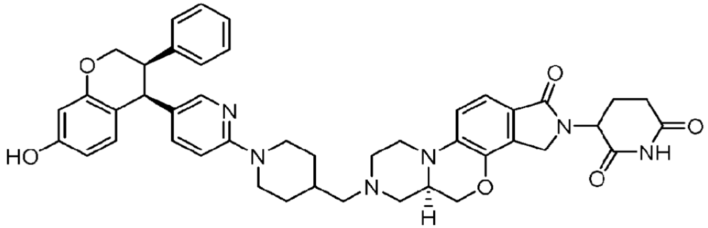
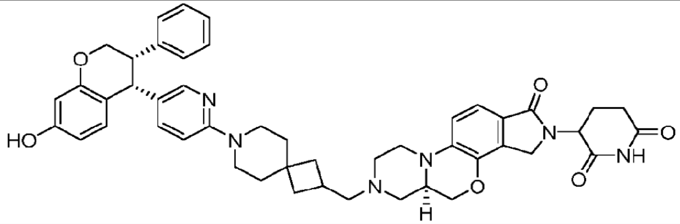
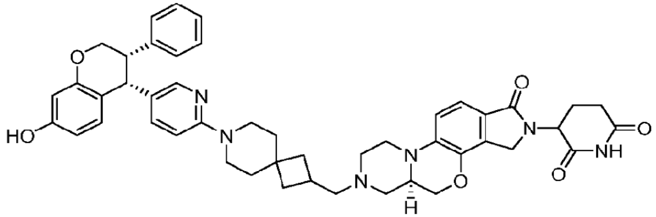
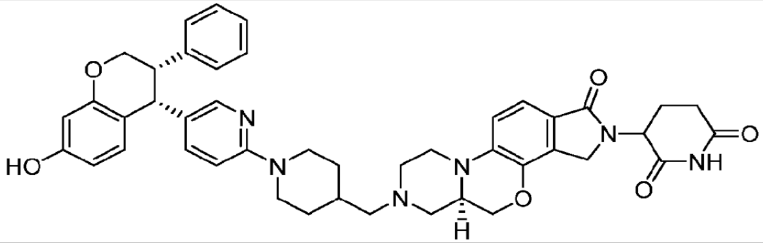
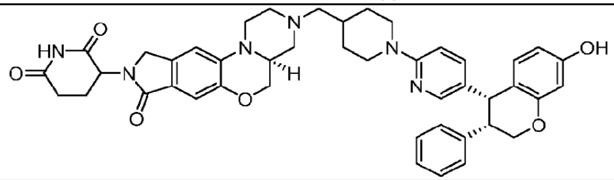
| **A64*** |  | 3-((R)-7-((1-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A65*** |  | 3-((R)-7-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A66*** |  | 3-((R)-7-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A69*** |  | 3-((R)-7-((1-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)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 |
| **A70*** |  | 3-((S)-3-((1-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H- |

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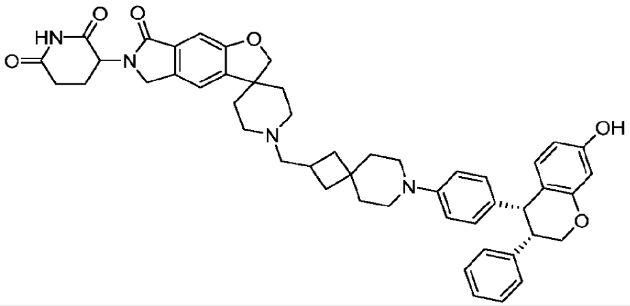
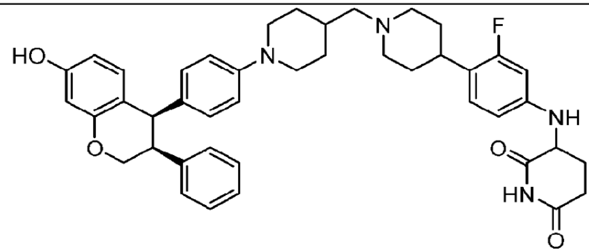
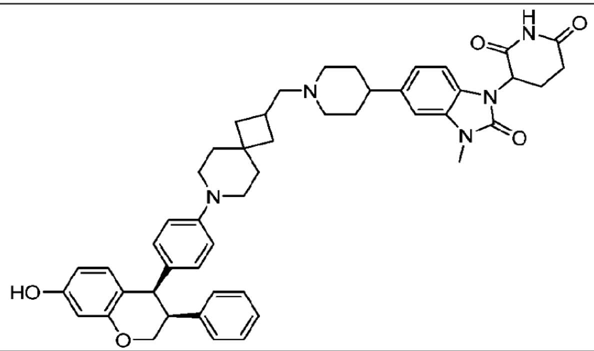
| | | pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione |
| **A71*** |  | 3-(1'-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione |
| **A72*** |  | 3-((3-fluoro-4-(1-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione |
| **A73*** |  | 3-(5-(1-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione |

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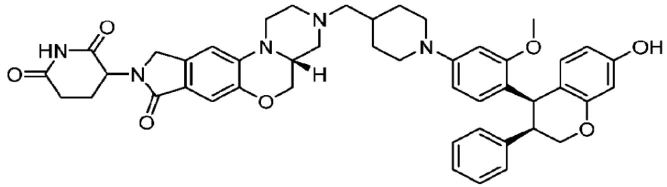
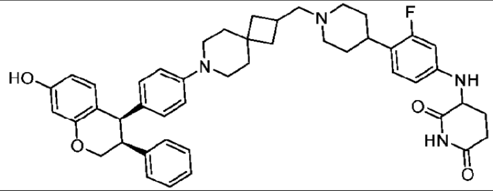
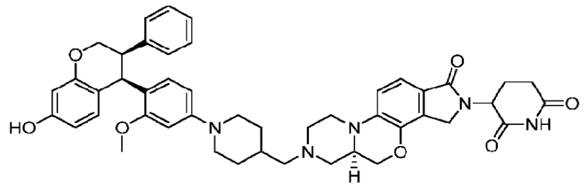
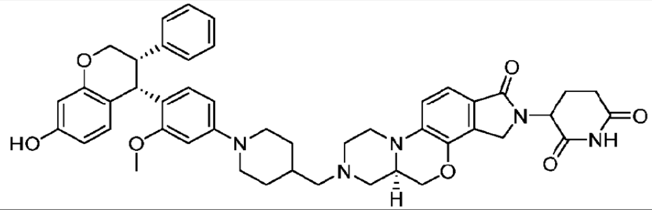
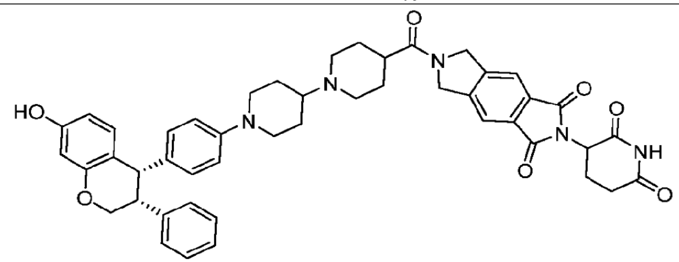
| **A74*** |  | 3-((R)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione |
| **A75*** |  | 3-((3-fluoro-4-(1-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione |
| **A76*** |  | 3-((R)-7-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-81pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A77*** |  | 3-((R)-7-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A78*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(1'-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |

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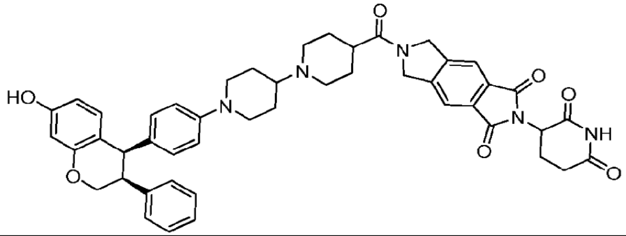
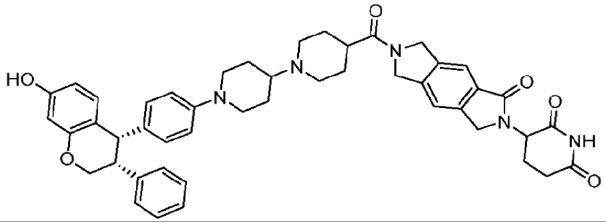
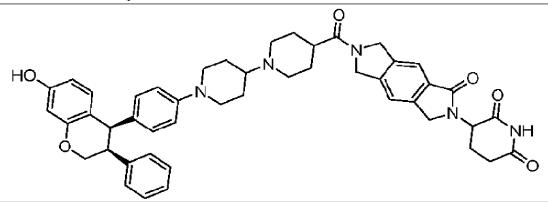
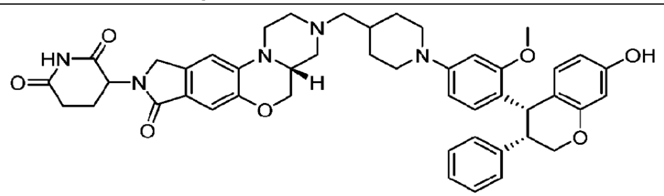
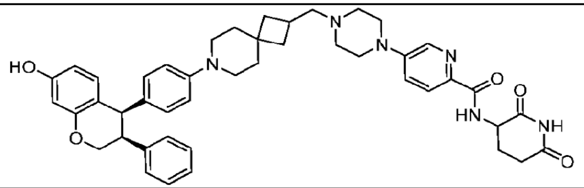
| **A79*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(1'-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |
| **A80*** |  | 3-(6-(1'-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione |
| **A81*** |  | 3-(6-(1'-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione |
| **A84*** |  | 3-((R)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A85*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)picolinamide |

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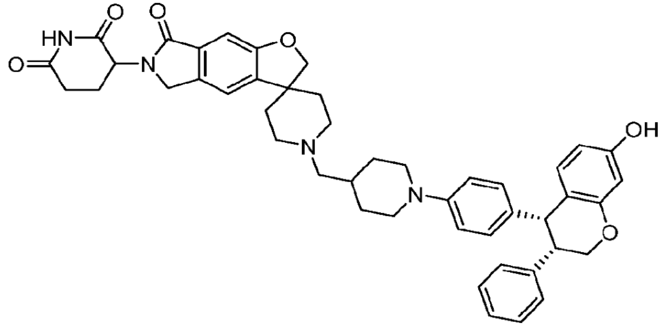
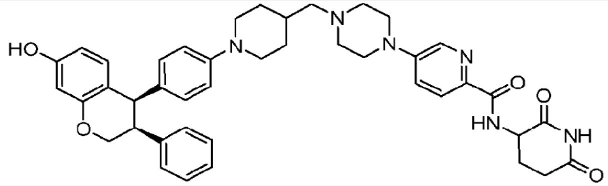
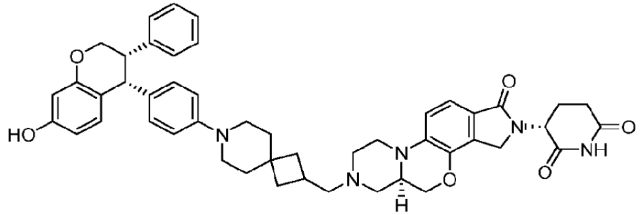
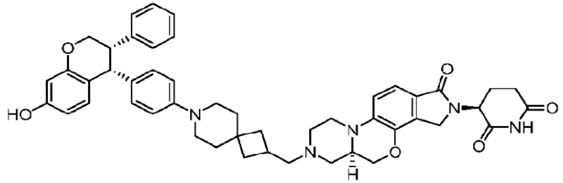
| **A86*** |  | 3-(1'-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione |
| **A88*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide |
| **A89*** |  | (R)-3-((R)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A90*** |  | (S)-3-((R)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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-c]isoindol-2-yl)piperidinc-2,6-dionc |

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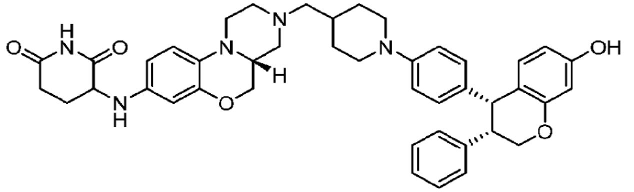
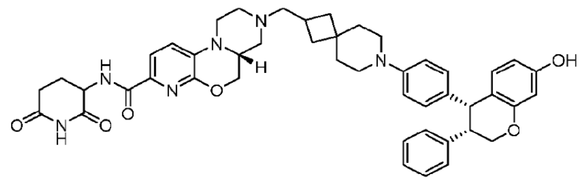
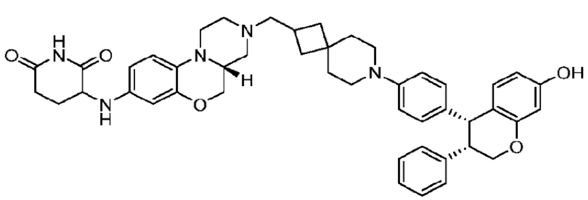
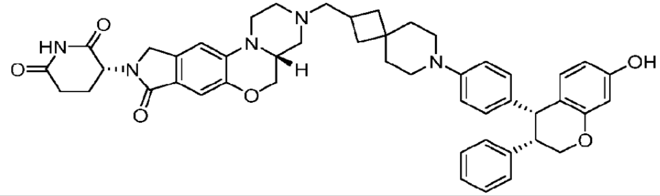
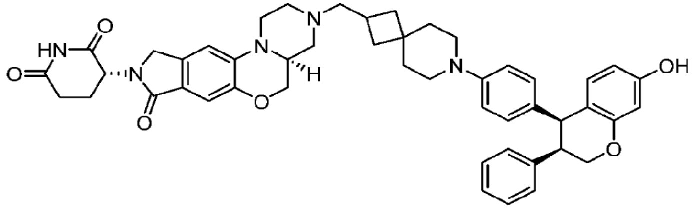
| A91* |  | 3-(((R)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazin-8-yl)amino)piperidine-2,6-dione hydrochloride |
| A93* |  | (4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide |
| A94* |  | 3-(((R)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazin-8-yl)amino)piperidine-2,6-dione |
| A95* |  | (R)-3-((R)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| A96* |  | (R)-3-((S)-3-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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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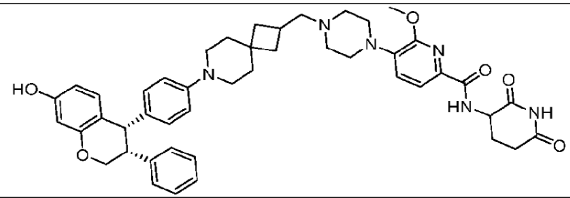
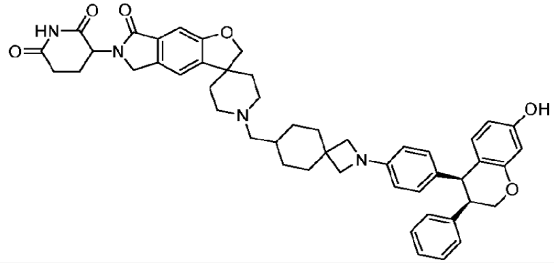
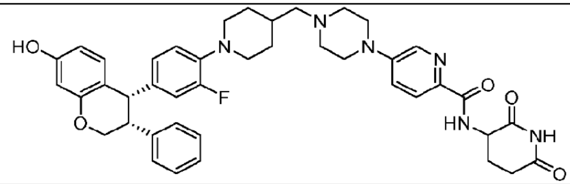
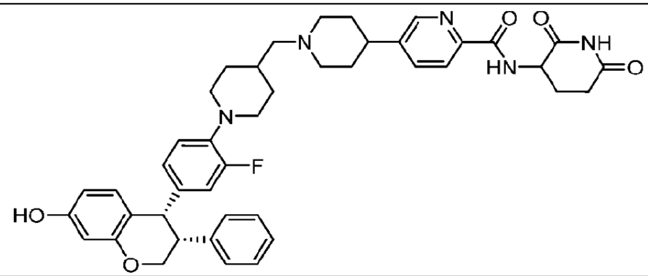
| **A97*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-6-methoxypicolinamide |
| **A99*** |  | 3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione |
| **A100*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide |
| **A101*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(1-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)picolinamide |

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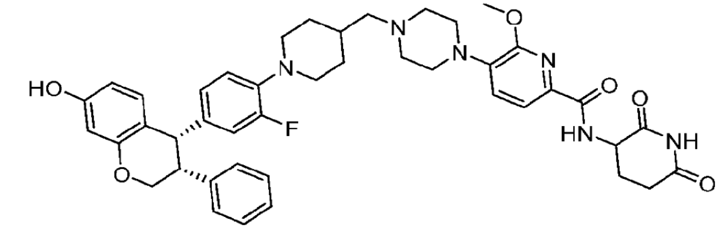
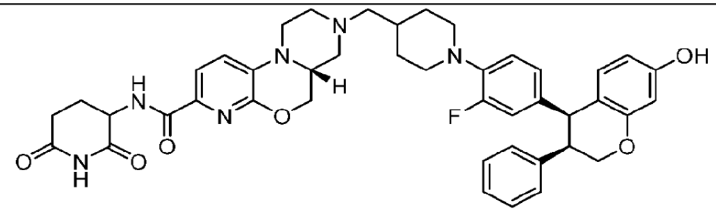
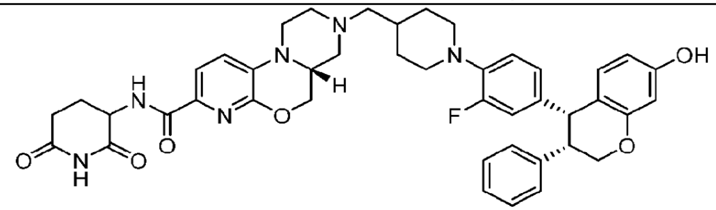
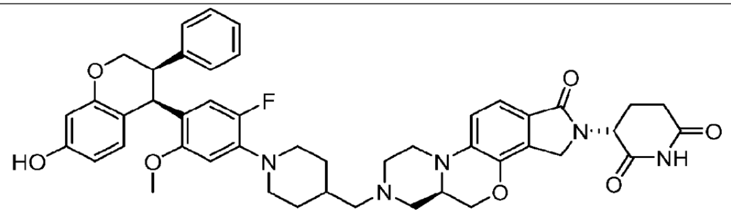
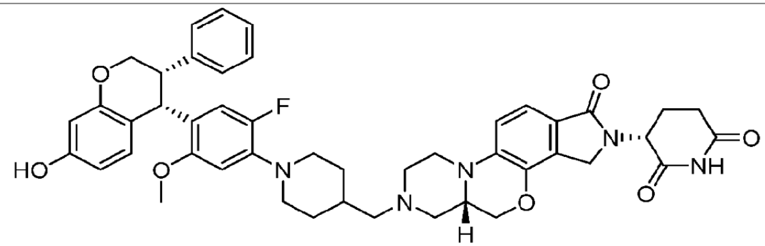
|---|---|---|
| **A102*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-6-methoxypicolinamide |
| **A103*** |  | (4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide |
| **A104*** |  | (4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A105*** |  | (R)-3-((S)-7-((1-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-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-2,7-dione |
| **A106*** |  | (R)-3-((S)-7-((1-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-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 |

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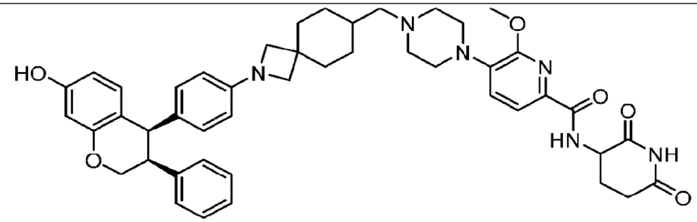
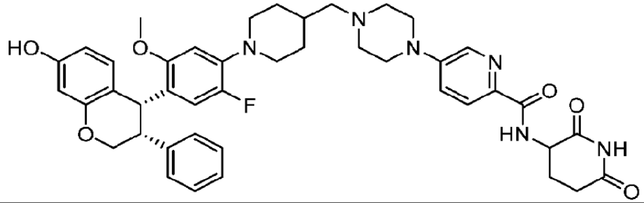
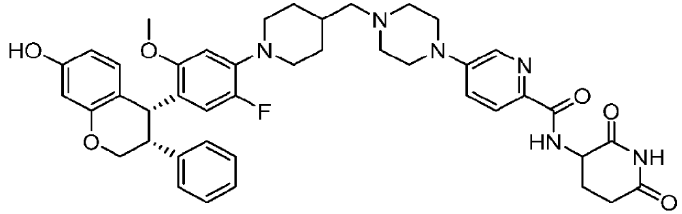
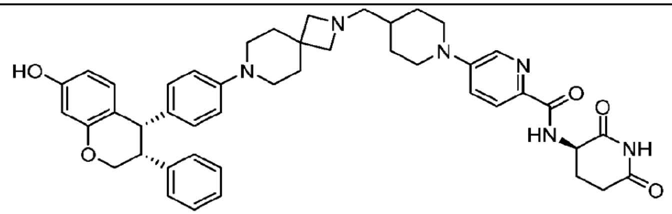
| **A108*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-6-methoxypicolinamide |
| **A109*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide |
| **A110*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide |
| **A111*** |  | N-((R)-2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)methyl)piperidin-1-yl)picolinamide |

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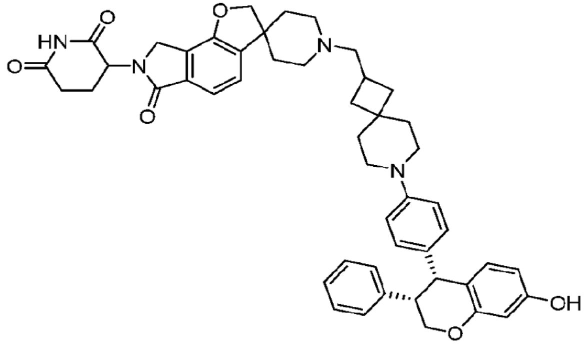
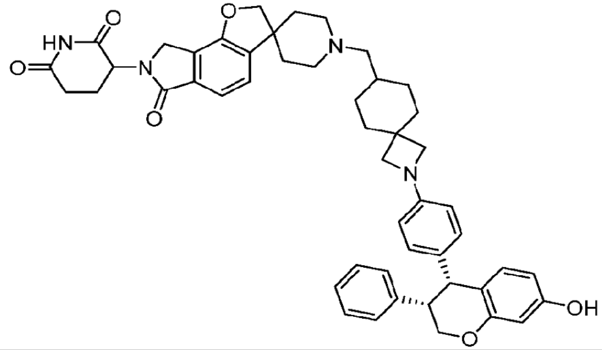
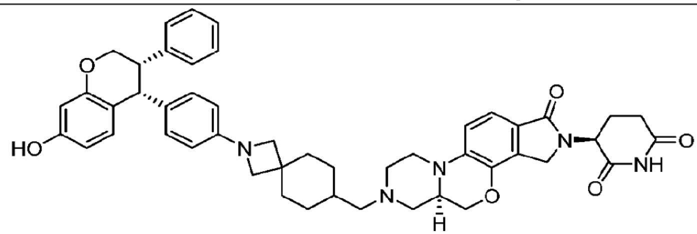
| **A113*** |  | 3-(1'-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione |
| **A114*** |  | 3-(1'-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione |
| **A115*** |  | (S)-3-((R)-7-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |

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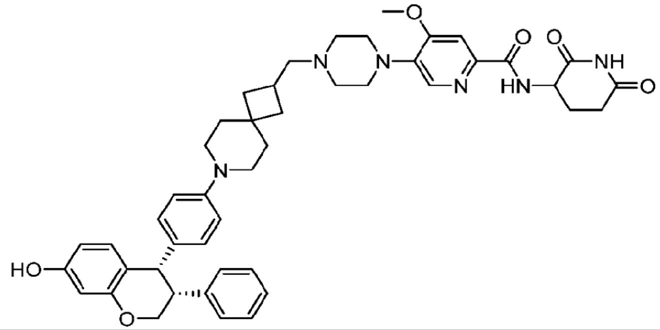
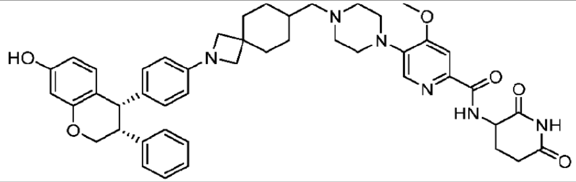
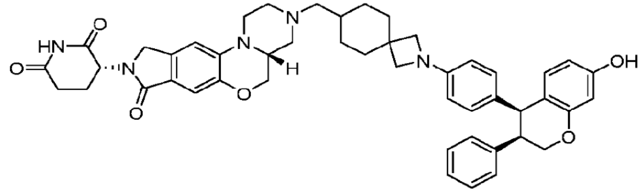
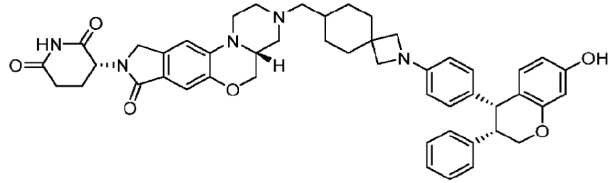
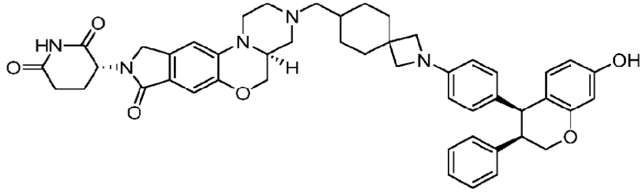
| **A116*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide |
| **A117*** |  | rac-N-(2,6-dioxopiperidin-3-yl)-5-(4-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide |
| **A118*** |  | (R)-3-((R)-3-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
| **A119*** |  | (R)-3-((R)-3-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A120*** |  | (R)-3-((S)-3-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |

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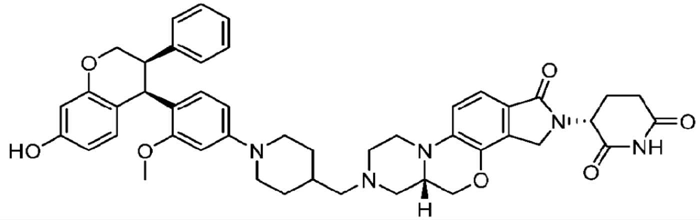
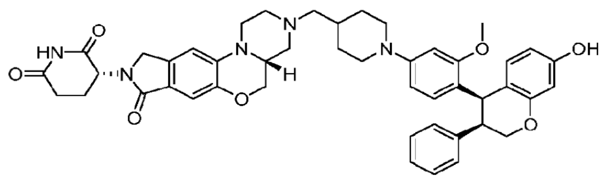
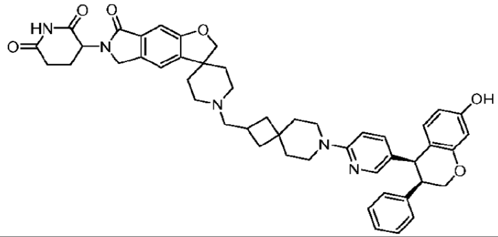
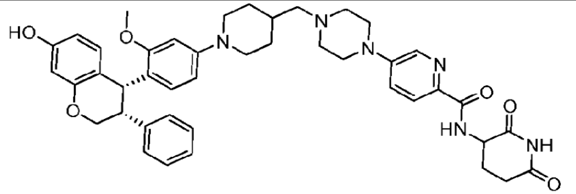
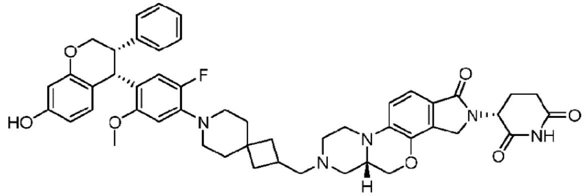
| **A121*** |  | (R)-3-((S)-7-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A122*** |  | (R)-3-((R)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione |
| **A123*** |  | 3-(1'-((7-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
| **A124*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide |
| **A125*** |  | (R)-3-((S)-7-((7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-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 |

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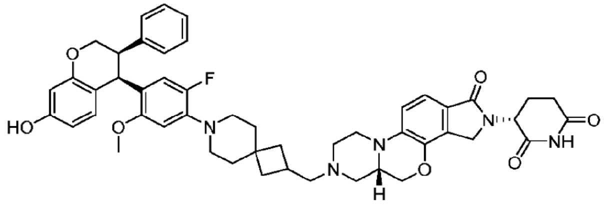
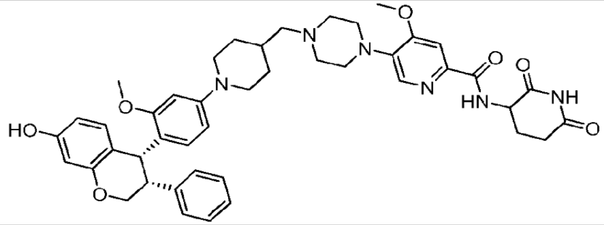
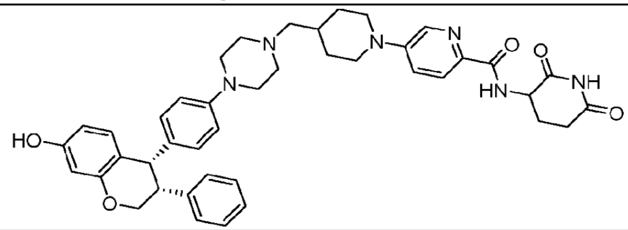
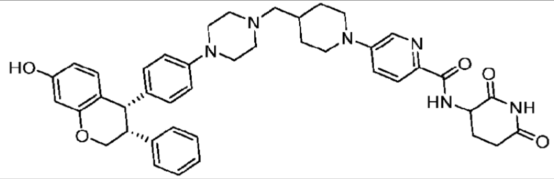
| **A126*** |  | (R)-3-((S)-7-((7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A127*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)mcthyl)pipcrazin-1-yl)-4-methoxypicolinamide |
| **A128*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((4-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)picolinamide |
| **A129*** |  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((4-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)picolinamide |

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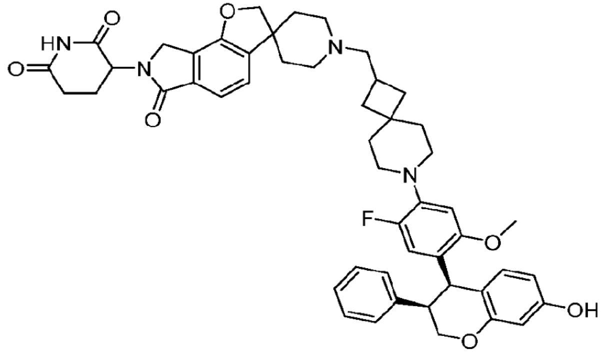
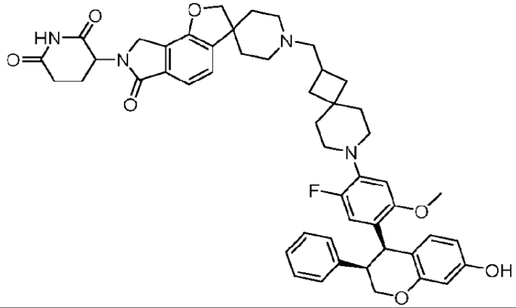
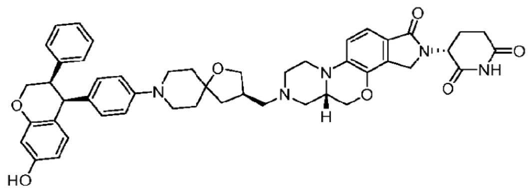
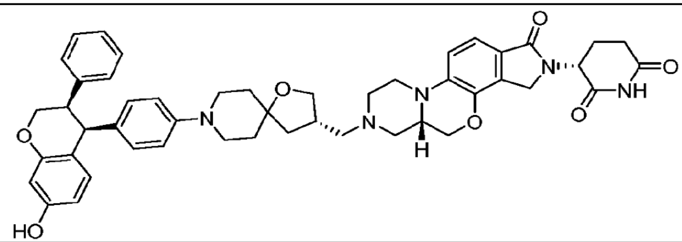
| **A130*** |  | 3-(1'-((7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione |
| **A131*** |  | 3-(1'-((7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione |
| **A132*** |  | (R)-3-((S)-7-(((R)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
| **A133*** |  | (R)-3-((S)-7-(((S)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |

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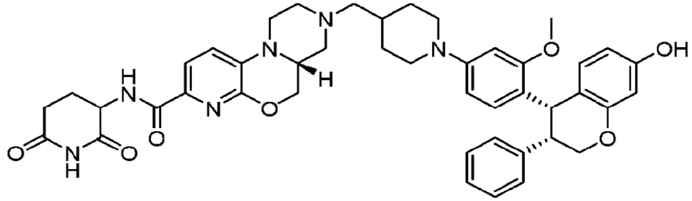
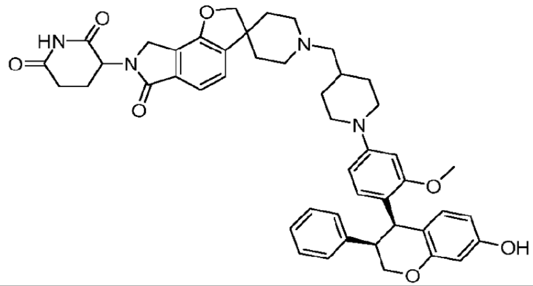
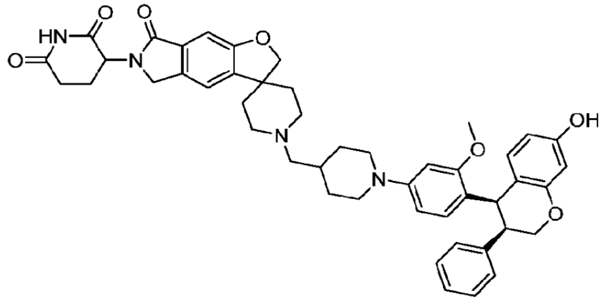
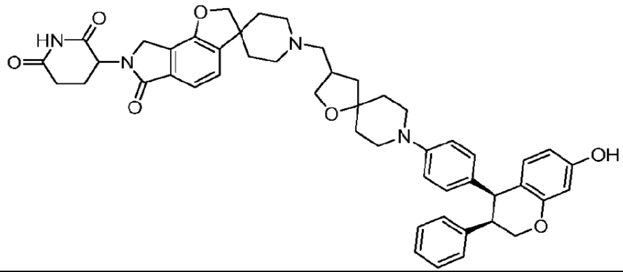
| **A134*** |  | (4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide |
| **A135*** |  | 3-(1'-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione |
| **A136*** |  | 3-(1'-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
| **A137*** |  | 3-(1'-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |

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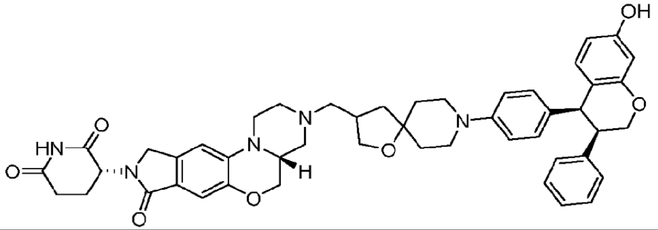
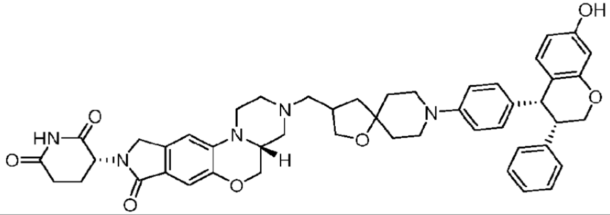
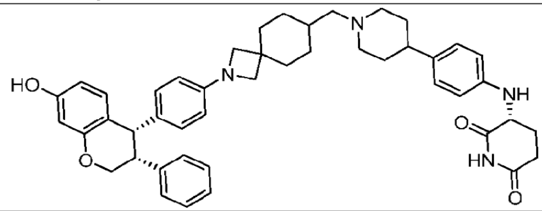
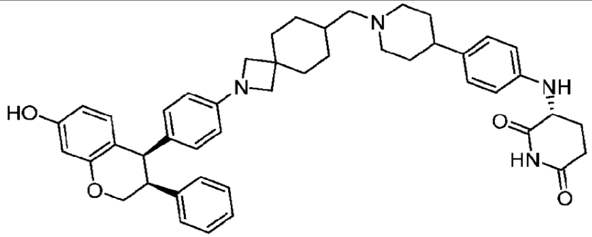
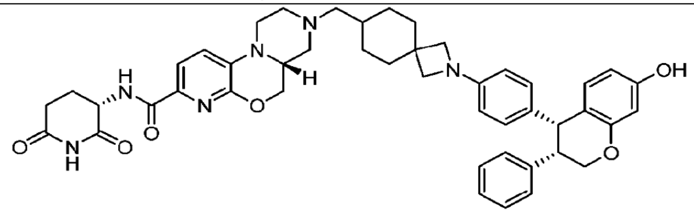
| **A138*** |  | (3R)-3-((4aR)-3-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione |
| **A139*** |  | (3R)-3-((4aR)-3-((8-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-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 |
| **A140*** |  | (R)-3-((4-(1-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione |
| **A141*** |  | (R)-3-((4-(1-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione |
| **A142*** |  | (R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-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 |

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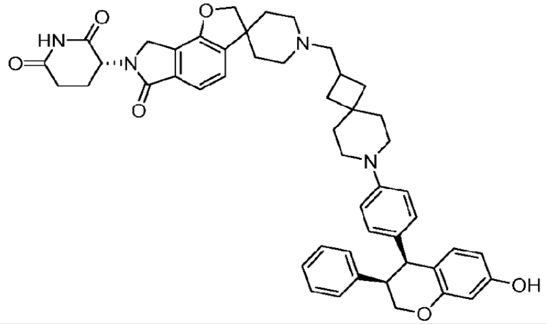
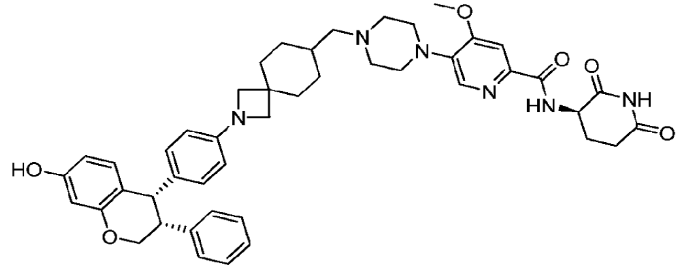
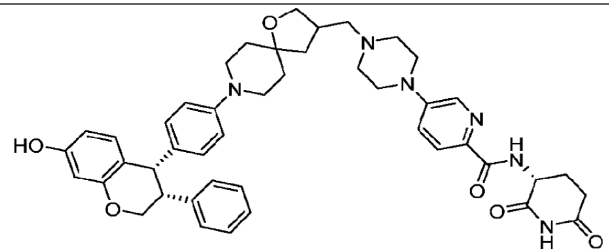
| **A143*** |  | (R)-3-(1'-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione |
| **A144*** |  | N-((R)-2,6-dioxopiperidin-3-yl)-5-(4-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide |
| **A145*** |  | N-((R)-2,6-dioxopiperidin-3-yl)-5-(4-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperazin-1-yl)picolinamide |

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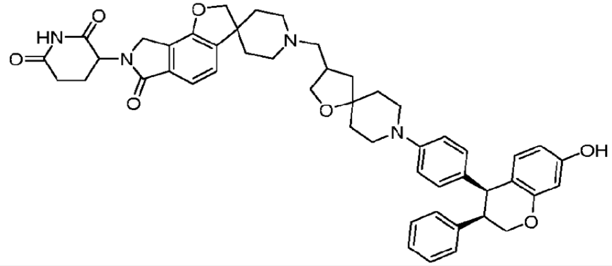
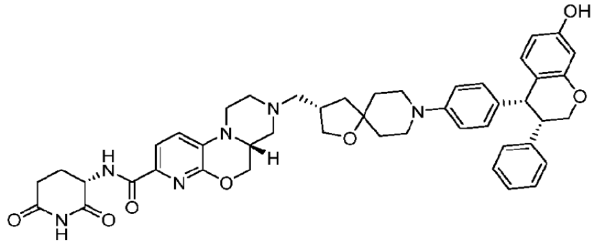
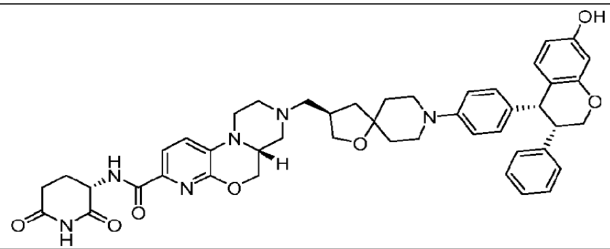
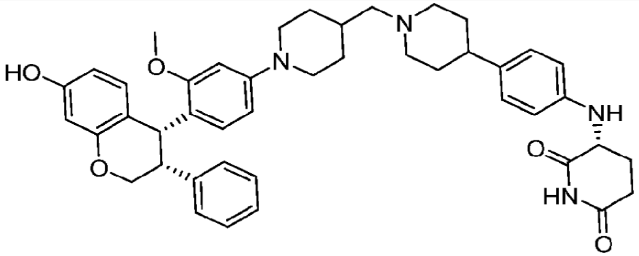
| **A146*** |  | 3-(1'-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione |
| **A147*** |  | (R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-(((S)-8-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide |
| **A148*** |  | (R)-N-((S)-2,6-dioxopiperidin-3-yl)-3-(((R)-8-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
| **A149*** |  | (R)-3-((4-(1-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione |

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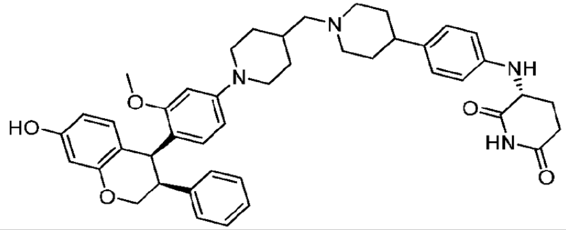
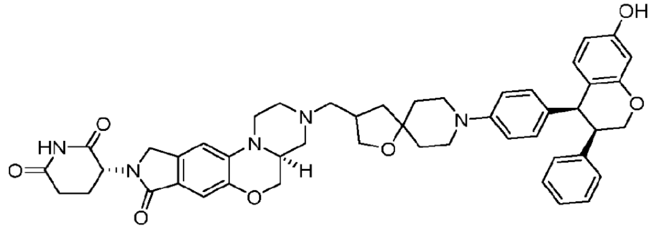
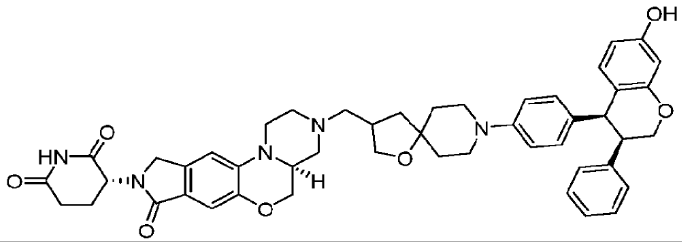
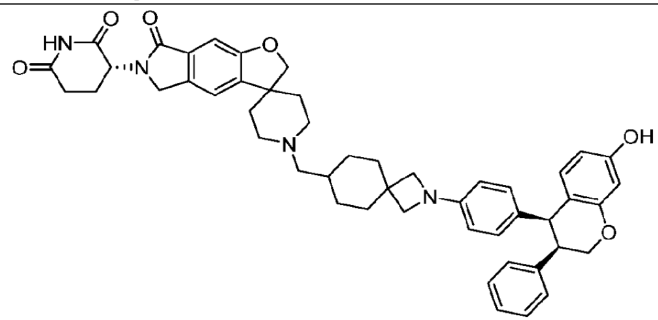
| **A150*** |  | (R)-3-((4-(1-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione |
| **A151*** |  | (R)-3-((S)-3-(((R)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione |
| **A152*** |  | (R)-3-((S)-3-(((S)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
| **A153*** |  | (R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |

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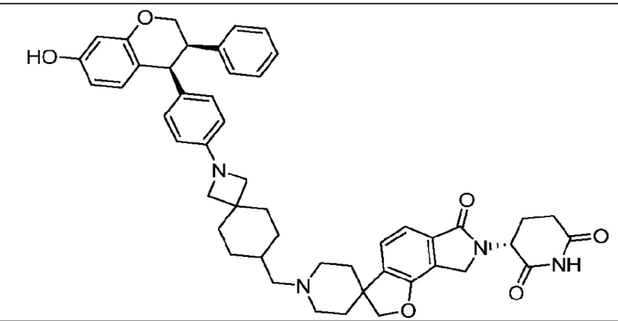
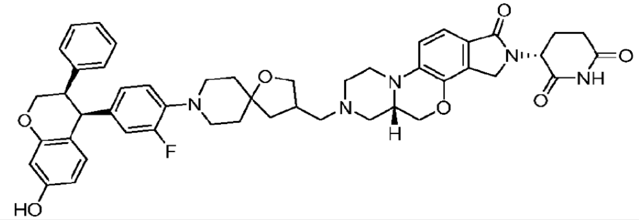
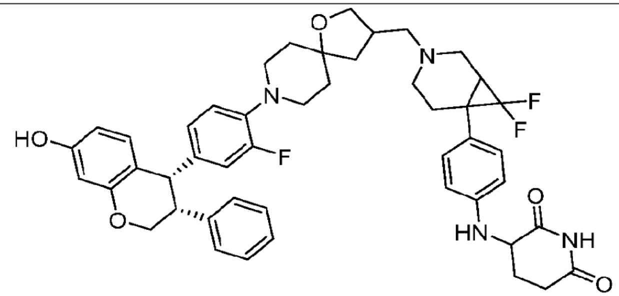
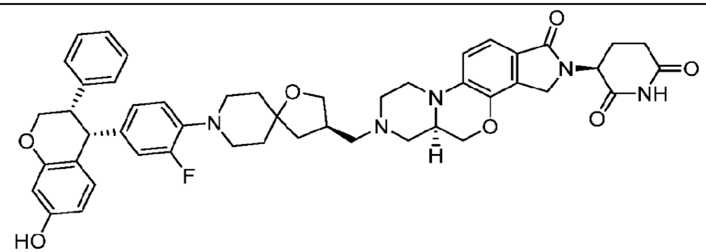
| **A154*** |  | (R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione |
| **A155*** |  | (R)-3-((S)-7-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A156*** |  | 3-((4-(7,7-difluoro-3-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
| **A157*** |  | (S)-3-((R)-7-(((R)-8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |

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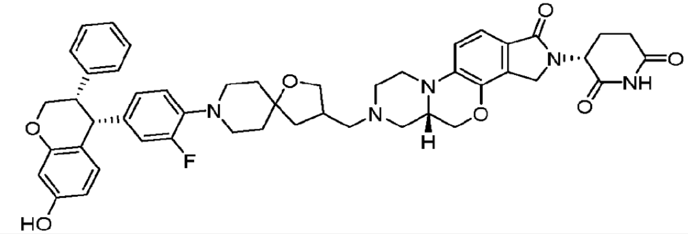
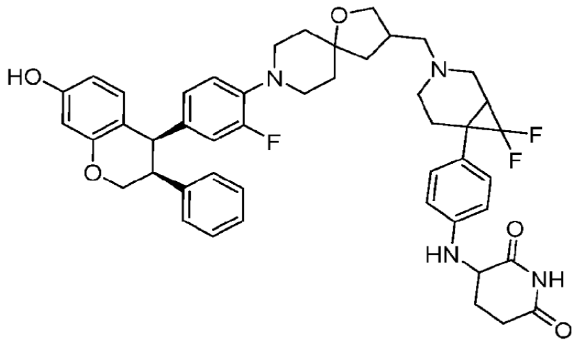
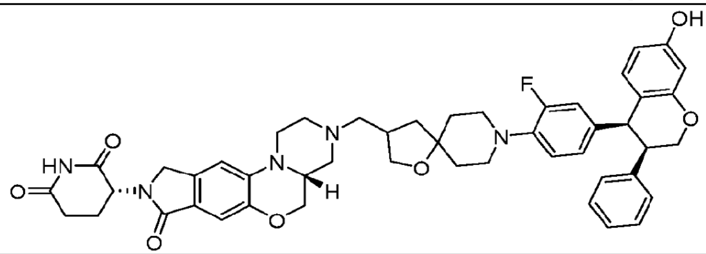
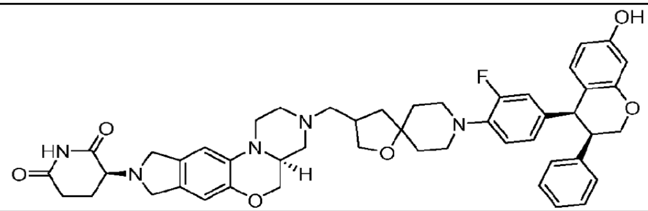
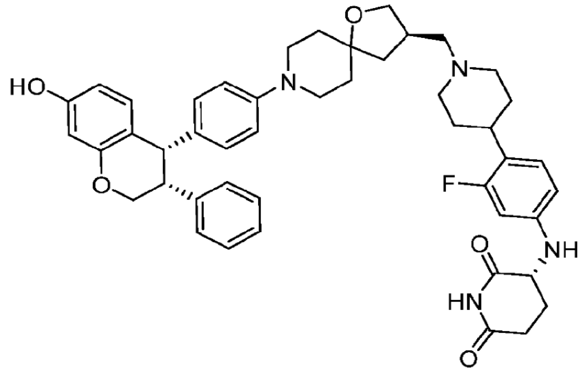
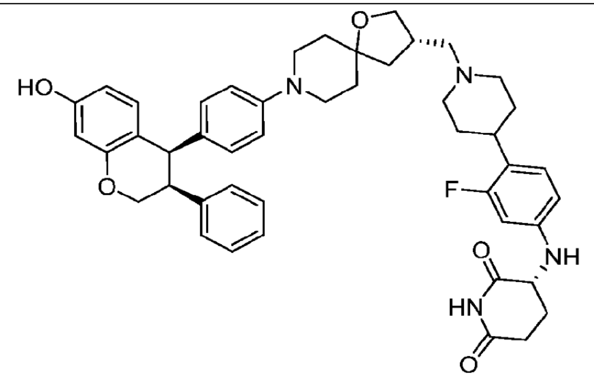
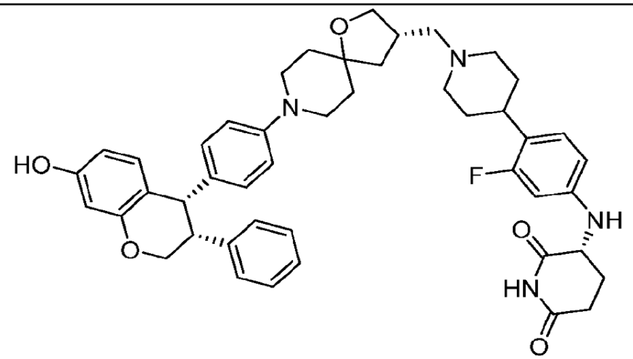
|---|---|---|
| **A158*** |  | (3R)-3-((5aS)-7-((8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione |
| **A159*** |  | 3-((4-(7,7-difluoro-3-(((R)-8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione |
| **A160*** |  | (R)-3-((R)-3-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
| **A161*** |  | (S)-3-((S)-3-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-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 |

| | | |
|---|---|---|
| **A162*** |  | (R)-3-((3-fluoro-4-(1-(((R)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione |
| **A163*** |  | (R)-3-((3-fluoro-4-(1-(((S)-8-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione |
| **A164*** |  | (R)-3-((3-fluoro-4-(1-(((S)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione |

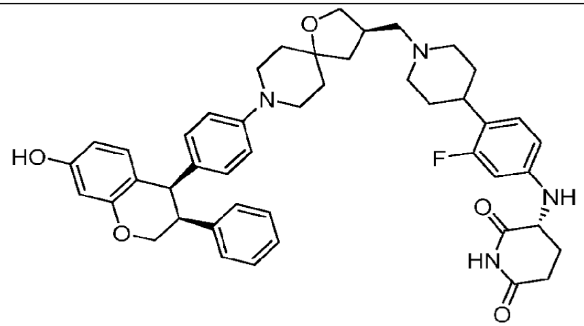
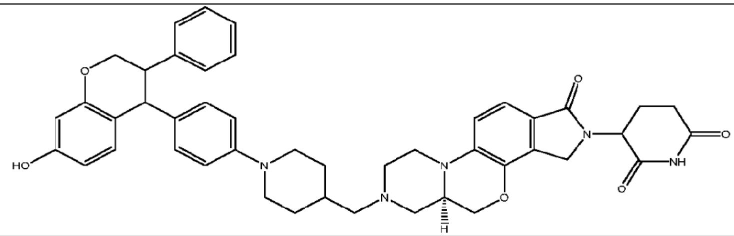
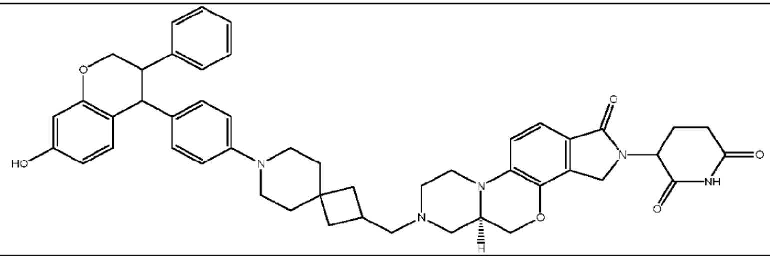
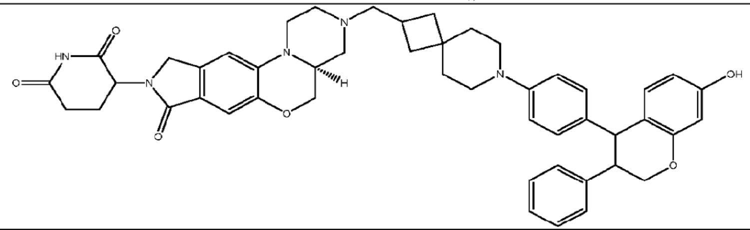
| | | |
|---|---|---|
| **A165*** |  | (R)-3-((3-fluoro-4-(1-(((R)-8-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione |

**Table 2. Compounds B1-B5**

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

| Compound No | Chemical Name | Chemical Name |
|---|---|---|
| **B1*** |  | 3-((5aR)-7-((1-(4-(7-hydroxy-3-phenylchroman-4-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 |
| **B2*** |  | 3-((5aR)-7-((7-(4-(7-hydroxy-3-phenylchroman-4-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 |
| **B3*** |  | 3-((4aS)-3-((7-(4-(7-hydroxy-3-phenylchroman-4-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 |

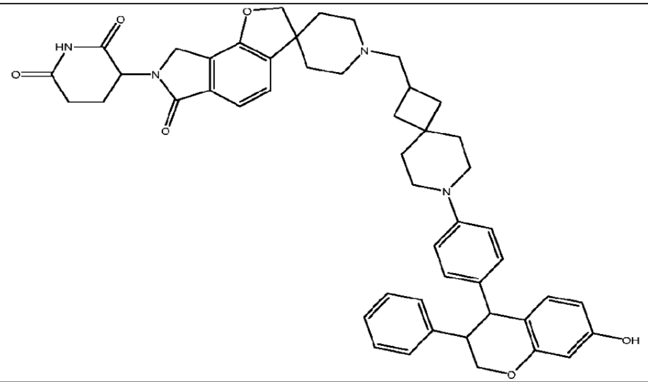
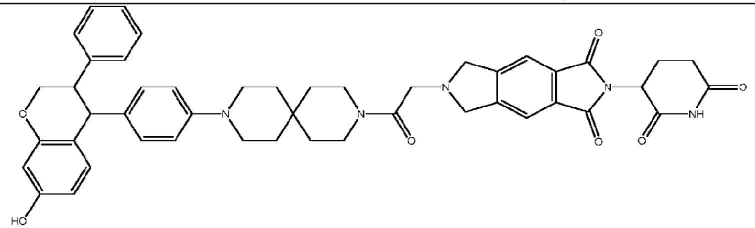
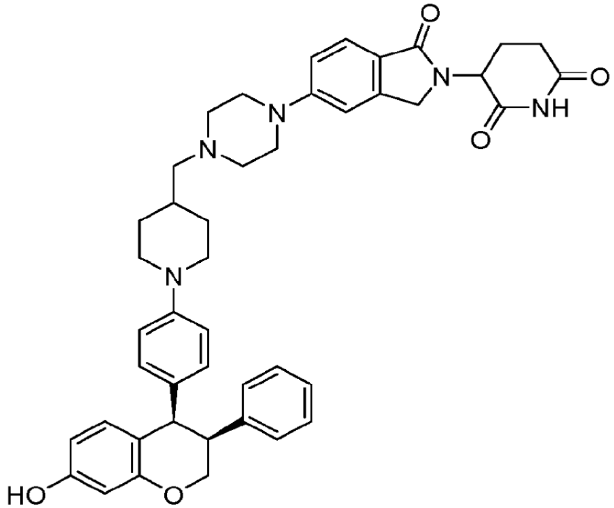
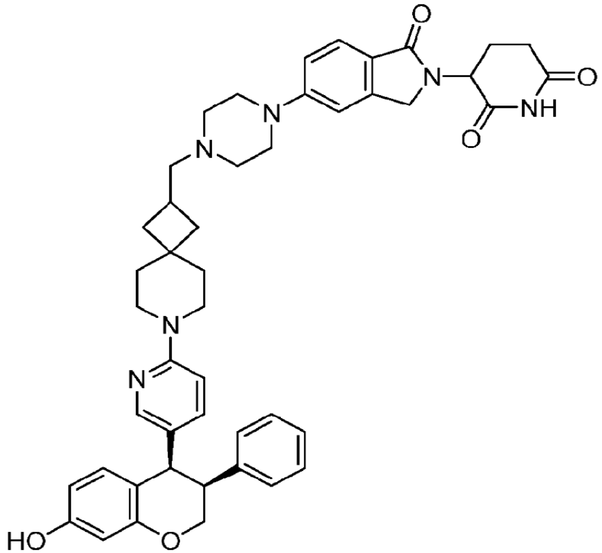
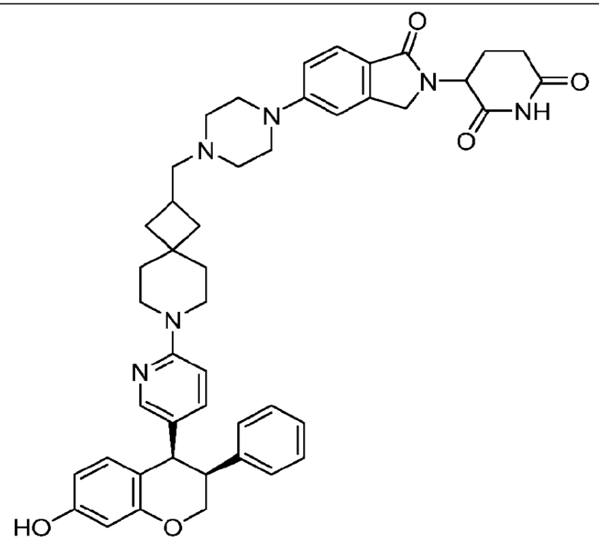
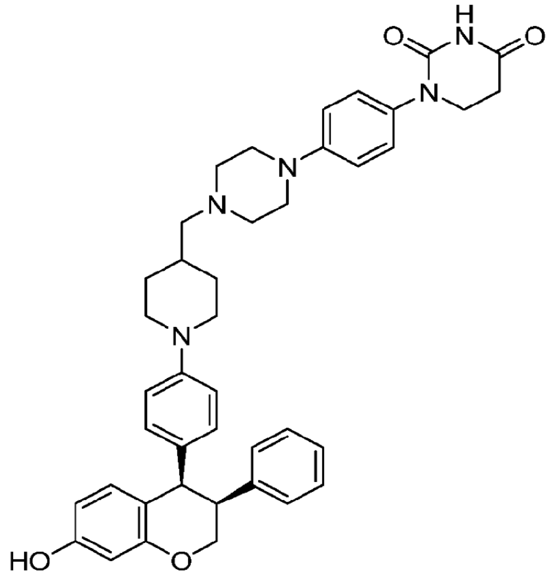
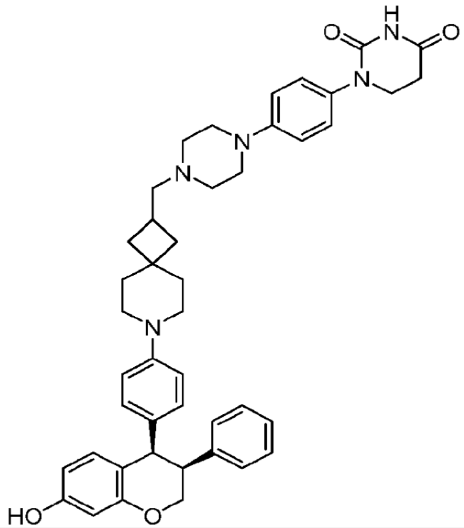
| | | |
|---|---|---|
| **B4*** |  | 3-(1'-((7-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione |
| **B5*** |  | 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |

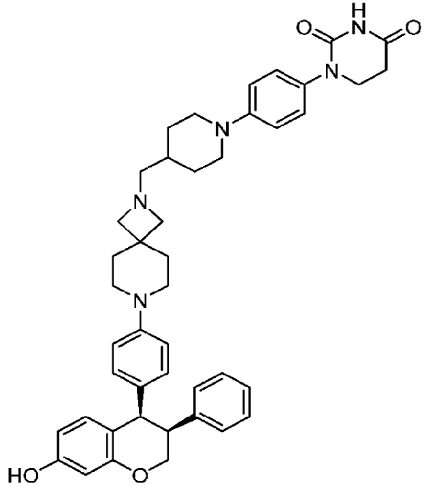
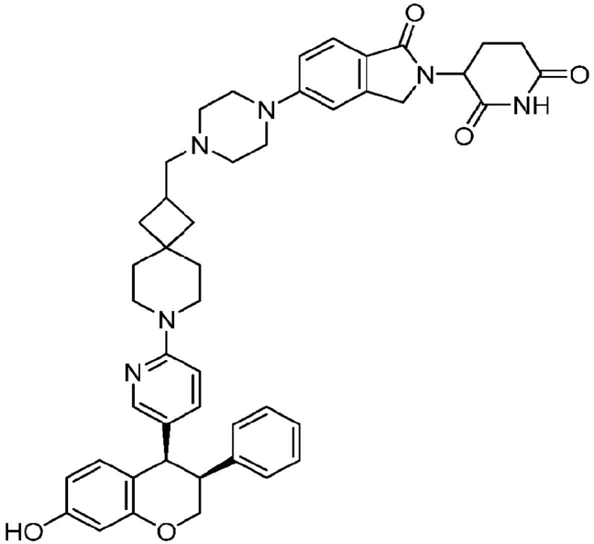
**Table 3. Selected Compounds from A1-A165**

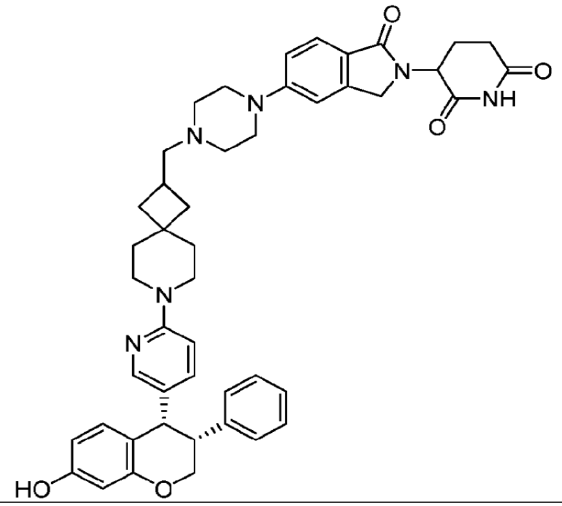
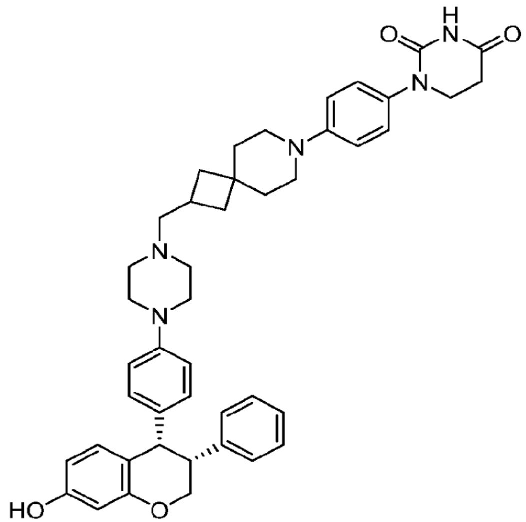
**designates that it is enantiomerically pure with respect to the warhead (chroman) but the absolute configuration is not specified; the relative configuration of the two stereogenic centers is* ***cis****.*

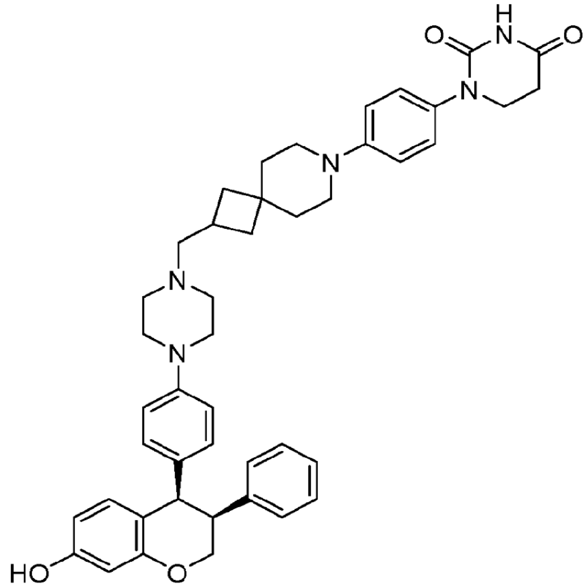
| Compound No | Chemical Name | Chemical Name |
|---|---|---|
| **A62*** |  | 3-(5-(4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione |

| | | |
|---|---|---|
| **A67*** |  | 3-(5-(4-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione |
| **A68*** |  | 3-(5-(4-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione |

| | | |
|---|---|---|
| **A82*** |  | 1-(4-(4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione |
| **A83*** |  | 1-(4-(4-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione |

| | | |
|---|---|---|
| **A87*** |  | 1-(4-(4-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)methyl)piperidin-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione |
| **A92*** |  | (R)-3-(5-(4-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione |

| | | |
|---|---|---|
| **A98*** |  | (R)-3-(5-(4-((7-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione |
| **A107*** |  | 1-(4-(2-((4-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperazin-1-yl)methyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione |

| | | |
|---|---|---|
| **A112*** |  | 1-(4-(2-((4-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperazin-1-yl)methyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione |

**[0124]** 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.

**[0125]** 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.

**[0126]** In some 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 some 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 some 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.

**[0127]** The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

## Forms of Compounds Disclosed Herein

*Pharmaceutically acceptable salts*

**[0128]** In some embodiments, the compounds disclosed herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

**[0129]** In some 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 some 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.

**[0130]** 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.

**[0131]** 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.

**[0132]** In some 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, $N^{+}(C_{1-4}\text{ alkyl})_4$, and the like.

**[0133]** 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 some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

*Solvates*

**[0134]** 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 present disclosure.

**[0135]** 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.

**[0136]** In some 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.

**[0137]** 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*

**[0138]** 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."

**[0139]** In some embodiments, the compounds described herein exist as geometric isomers. In some 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 present disclosure.

**[0140]** In some 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 present disclosure.

**[0141]** 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 some 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 some embodiments, dissociable complexes are preferred. In some 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 some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent.

*Tautomers*

**[0142]** In some embodiments, compounds described herein exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein.

**[0143]** 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. All tautomeric forms of the compounds disclosed herein are contemplated and are within the scope of the present disclosure. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

## Pharmaceutical Compositions

**[0144]** 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, 21$^{st}$ Ed. Mack Pub. Co., Easton, PA (2005)).

**[0145]** 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.

**[0146]** 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.

**[0147]** 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.

**[0148]** 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.

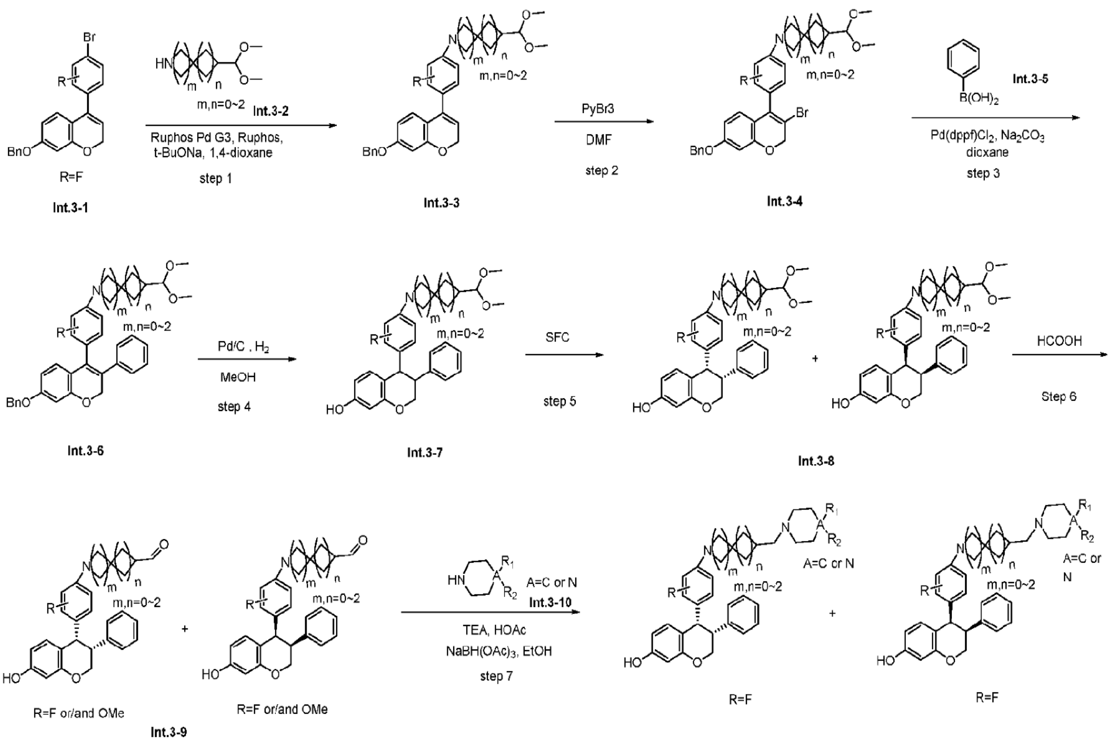
## Preparation of the Compounds

**[0149]** 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*

**[0150]** 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**



**[0151]** 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).

**[0152]** 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).

**[0153]** 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.

**[0154]** 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*

**[0155]** Unless otherwise noted, reagents and solvents were 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*

**[0156]** The biological activities of the compounds of the present application can be assessed with methods and assays known in the art.

**[0157]** 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 on Envision reader (Perkin Elemer).

**[0158]** 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 at cold room. 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 are captured on Odyssey® DLx Imaging System.

**[0159]** In vitro assay can be accompolished by MCF-7 and T47D Cell Titer Glo (CTG) assay. MCF-7 and T47D cell (From HDB) are cultured in 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 are treated with compound at certain concentrations (e.g., 0.5 to 10000 nM) (DMSO and Staurosporine as control). On day 0 and day 6: add Cell Titer Glo reagent and read on EnVision after 30min incubation for data generation.

**[0160] 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 a 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 were obtained by comparing the values of treated wells to those in untreated and DMSO-treated wells as 100%.

**[0161] Western Blot Analysis.** The 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.

**[0162] Cell Growth Assay**. The cells are seeded at certain concentration (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 incubate 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.

**[0163] In vivo pharmacodynamic and efficacy studies.** To develop breast cancer cell line xenografts, mice are given 17β-Estradiol in drinking water for a certain period of time. Certain number (e.g., five million) of cells in 50% Matrigel are injected subcutaneously into SCID mice to induce tumor formation. When tumors reach 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 indicated 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**

**[0164]** 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.

**[0165]** 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.

**[0166]** In certain aspects, the present disclsoure provides compounds disclosed herein for use in degrading an estrogen receptor in a subject.

[0167] 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).

[0168] 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).

[0169] 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.

[0170] 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.

[0171] 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.

[0172] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating a disease or disorder in a subject in need thereof.

[0173] In certain embodiments, the disease or disorder is an estrogen receptor-mediated disease or disorder.

[0174] In certain embodiments, the disease or disorder is cancer.

[0175] In certain embodiments, the disease or disorder is breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or esophageal cancer.

[0176] 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 | | | |

**[0177]** 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 | |

**[0178]** In certain embodiments, the subject is a mammal.

**[0179]** In certain embodiments, the subject is a human.

**[0180]** In certain embodiments, the subject is a biological sample (e.g., a cell population).

## Definitions

**[0181]** As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

*Chemical Definitions*

**[0182]** 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, 75$^{th}$ 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, 5$^{th}$ 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, 3$^{rd}$ Edition, Cambridge University Press, Cambridge, 1987.

**[0183]** 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).

**[0184]** The present disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

**[0185]** 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.

**[0186]** 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 invention, 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 to 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.

**[0187]** "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 ($-CH_2CH(CH_3)_2$).

**[0188]** "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.

**[0189]** "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.

**[0190]** "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.

**[0191]** "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.

**[0192]** "Alkynylene" as used herein, refers to a linear 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.

**[0193]** 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 ("hetero$C_{1-10}$ alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1, 2, 3, or 4 heteroatoms ("hetero$C_{1-9}$ alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1, 2, 3, or 4 heteroatoms ("hetero$C_{1-8}$ alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1, 2, 3, or 4 heteroatoms ("hetero$C_{1-7}$ alkyl"). In certain embodiments, a heteroalkyl group is a group having 1 to 6 carbon atoms and 1, 2, or 3 heteroatoms ("hetero$C_{1-6}$ alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms ("hetero$C_{1-5}$ alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and/or 2 heteroatoms ("hetero$C_{1-4}$ alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom ("hetero$C_{1-3}$ alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom ("hetero$C_{1-2}$ alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("hetero$C_{1}$ alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms ("hetero$C_{2-6}$ alkyl"). 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 hetero$C_{1-10}$ alkyl. In certain embodiments, the heteroalkyl group is a substituted hetero$C_{1-10}$ alkyl.

**[0194]** 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 ("hetero$C_{2-10}$ alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1, 2, 3, or 4 heteroatoms ("hetero$C_{2-9}$ alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms ("hetero$C_{2-8}$ alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms ("hetero$C_{2-7}$ alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1, 2, or 3 heteroatoms ("hetero$C_{2-6}$ alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms ("hetero$C_{2-5}$ alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and lor 2 heteroatoms ("hetero$C_{2-4}$ alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom ("hetero$C_{2-3}$ alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms ("hetero$C_{2-6}$ alkenyl"). 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 hetero$C_{2-10}$ alkenyl. In certain embodiments, the heteroalkenyl group is a substituted hetero$C_{2-10}$ alkenyl.

**[0195]** 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 is 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 ("hetero$C_{2-10}$ alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("hetero$C_{2-9}$ alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("hetero$C_{2-8}$ alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("hetero$C_{2-7}$ alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1, 2, or 3 heteroatoms ("hetero$C_{2-6}$ alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms ("hetero$C_{2-5}$ alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and lor 2 heteroatoms ("hetero$C_{2-4}$ alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom ("hetero$C_{2-3}$ alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms ("hetero$C_{2-6}$ alkynyl"). 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 hetero$C_{2-10}$ alkynyl. In certain embodiments, the heteroalkynyl group is a substituted hetero$C_{2-10}$ alkynyl.

**[0196]** 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.

**[0197]** "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 $\pi$ 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).

**[0198]** 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.

**[0199]** "Aralkyl" is a subset of alkyl and aryl, as defined herein, and refers to an optionally substituted alkyl group substituted by an optionally substituted aryl group.

**[0200]** "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 $\pi$ 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.

**[0201]** "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).

**[0202]** 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.

**[0203]** Exemplary 5-membered heteroaryl containing one heteroatom include, 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.

**[0204]** "Heteroaralkyl" is a subset of alkyl and heteroaryl, as defined herein, and refers to an optionally substituted alkyl group substituted by an optionally substituted heteroaryl group.

**[0205]** "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.

**[0206]** 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.

**[0207]** As the foregoing examples illustrate, 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.

**[0208]** “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 ring system. When substitution is indicated, unless otherwise specified, substitution can occur on any of the fused rings.

**[0209]** “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 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 the carbocyclyl rings in which the spiro structure is embeded.

**[0210]** “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.

**[0211]** "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.

**[0212]** 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.

**[0213]** As the foregoing examples illustrate, 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.

**[0214]** "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.

**[0215]** "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.

**[0216]** "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.

**[0217]** "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, and 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.

**[0218]** "Acyl" as used herein, refers to a radical -C(O)R, wherein R is hydrogen, substituted or unsubstitued alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstitued heteroaryl, as defined herein. Representative acyl groups include, but are not limited to, formyl (-CHO), acetyl (-C(=O)$CH_3$), cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl (-C(=O)Ph), and benzylcarbonyl (-C(=O)$CH_2$Ph).

**[0219]** "Acylamino" as used herein, refers to a radical -NRC(=O)R, wherein each instance of R is independently hydrogen, substituted or unsubstitued alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstitued heteroaryl, as defined herein. Exemplary "acylamino" groups include, but are not limited to, formylamino, acetylamino, cyclohexylcarbonylamino, cyclohexylmethyl-carbonylamino, benzoylamino and benzylcarbonylamino.

**[0220]** "Acyloxy" as used herein, refers to a radical -OC(=O)R, wherein R is hydrogen, substituted or unsubstitued alkyl, substituted or unsubstitued alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstitued carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstitued heteroaryl, as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl and benzylcarbonyl.

**[0221]** "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.

**[0222]** "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.

**[0223]**

**[0224]** "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.

**[0225]** "Azido" refers to the radical $-N_3$.

**[0226]** "Amino" refers to the radical $-NH_2$.

**[0227]** "Hydroxy" refers to the radical -OH.

**[0228]** "Thioketo" refers to the group =S.

**[0229]** "Carboxy" refers to the radical -C(=O)OH.

**[0230]** "Cyano" refers to the radical -CN.

**[0231]** "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.

**[0232]** "Nitro" refers to the radical $-NO_2$.

**[0233]** "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.

**[0234]** 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)).

**[0235]** 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)).

**[0236]** Common types of thiol-protecting groups include but not limited to sulfide (*e.g.*, p-methylbenzyl (Meb), *t*-butyl, acetamidomethyl (Acm), and triphenylmethyl (Trityl)).

**[0237]** 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.

**[0238]** These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

*Other Definitions*

[0239] As used herein, “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.

[0240] As used herein, “pharmaceutically acceptable salt” refers to a salt of a compound of the present 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 base addition salts. Specifically, such salts include: (1) acid addition salts, formed 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.

[0241] As used herein, the term “pharmaceutically acceptable cation” refers to an acceptable cationic counterion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like (see, *e.g.*, Berge, et al., J. Pharm. Sci. 66 (1):1-79 (January 77).

[0242] As used herein, “Pharmaceutically acceptable vehicle” refers to a diluent, adjuvant, excipient or carrier with which a compound of the present disclosure is administered.

**[0243]** As used herein, "pharmaceutically acceptable metabolically cleavable group" refers to a group which is cleaved *in vivo* to yield the parent molecule of the structural formula indicated herein. Examples of metabolically cleavable groups include -COR, -COOR, -$CONR_2$ and -$CH_2OR$ radicals, where R is selected independently at each occurrence from alkyl, trialkylsilyl, carbocyclic aryl or carbocyclic aryl substituted with one or more of alkyl, halogen, hydroxy or alkoxy. Specific examples of representative metabolically cleavable groups include acetyl, methoxycarbonyl, benzoyl, methoxymethyl and trimethylsilyl groups.

**[0244]** As used herein, "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 present 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.

**[0245]** As used herein, 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.

**[0246]** As used herein, an "effective amount" means the amount of a compound that, when administered to a subject for treating or preventing a disease, is sufficient to effect 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.

**[0247]** As used herein, "subject in need thereof" refers to a subject having a disease or having an increased risk of developing the disease. A subject in need thereof can be one who has previously been diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (i.e., a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a refractory or resistant disease or disorder disclosed herein (i.e., a disease or disorder disclosed herein that does not respond or has not yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

**[0248]** As used herein, "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).

**[0249]** As used herein, 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.

**[0250]** As used herein, "treating" or "treatment" or "therapeutic treatment" of any disease or disorder refers, in some 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 some embodiments, "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In some 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.

**[0251]** 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 only differ in the arrangement of their atoms in space are termed "stereoisomers."

**[0252]** 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".

**[0253]** As used herein "tautomers" refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of it electrons and an atom (usually H). 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.

**[0254]** 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.

**[0255]** 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.

**[0256]** 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.

**[0257]** 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.

**[0258]** 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.

**[0259]** As used herein, 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.

**[0260]** As used herein, 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.

**[0261]** As used herein, 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 some embodiments, to A only (optionally including elements other than B); in some embodiments, to B only (optionally including elements other than A); in some embodiments, to both A and B (optionally including other elements); etc.

**[0262]** 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.

**[0263]** 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 some embodiments, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in some embodiments, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in some 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.

**[0264]** 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.

**[0265]** 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.

**[0266]** 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

**[0267]** 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.

**[0268]** It is understood that the values presented in the examples are approximate values, and they are subject to instrumental and/or experimental variations.

## I. SYNTHESIS AND CHARACTERIZATION OF INTERMEDIATES AND COMPOUNDS A1-A165

**[0269]** 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.

**[0270]** 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.

**[0271]** 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 ºC

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 ºC

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.

**[0272]** 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.

**[0273]** 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.

**[0274]** 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.

**[0275]** Preparative reverse-phase high performance liquid chromatography (RP HPLC) was performed on either:

*METHOD 1.*

**[0276]** 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.*

**[0277]** 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

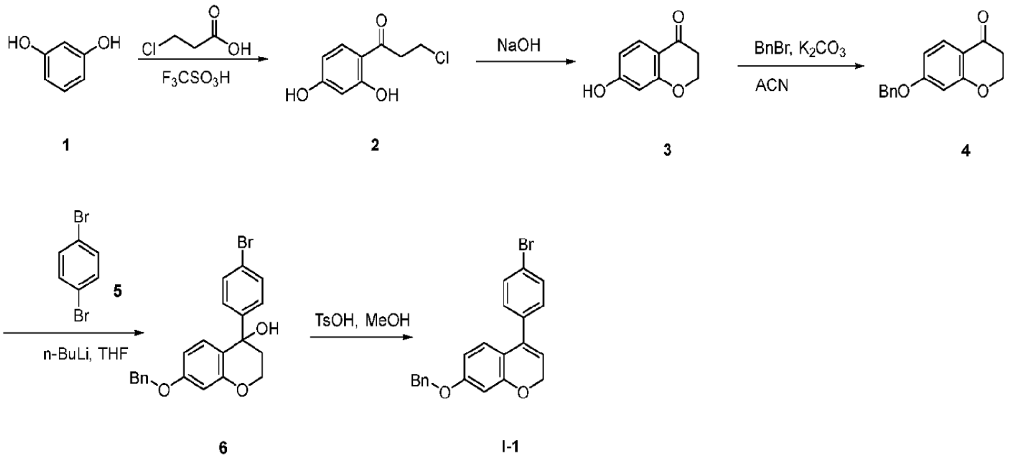
**[0278]** Nuclear magnetic resonance (NMR) spectra were recorded using Brucker AVANCE NEO 400 MHz at around 20 - 30°C unless otherwise specified. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublet; 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.

**[0279]** 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.

**[0280]** 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).

**[0281]** Compounds designated as R* or S* are enantiopure compounds where the absolute configuration was not determined.

**Intermediate 1: 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene**



*Step 1: 3-chloro-l-(2,4-dihydroxyphenyl)propan-l-one*

**[0283]** To a solution of resorcinol (110 g, 1.0 mol, 1.0 eq) and 3-chloropropanoic acid (120 g, 1.1 mol, 1.1 eq) at 40°C was added $CF_3SO_3H$ (500 g, 3.6 mol, 320 mL, 3.50 eq). The mixture was stirred at 80°C for 1 hour, cool to rt, and poured into ice-water (3 L). The precipitate was collected by filtration to afford 3-chloro-l-(2,4-dihydroxyphenyl)propan-l-one (200 g, 100% crude yield).

*Step 2: crude 7-hydroxychroman-4-one*

**[0284]** The crude 3-chloro-l-(2,4-dihydroxyphenyl)propan-l-one (200 g, 1.0 mol, 1.0 eq) was mixed with NaOH (160 g, 4.0 mol, 4.0 eq) in $H_2O$ (1.0 L), then the mixture was stirred at 0° C for 1 hour. The reaction mixture was first adjusted to pH = 5 with 6 N HCl, then extracted with EtOAc (2 x 500 mL). The organic layers were combined, dried over $Na_2SO_4$, filtrated, and concentrated under reduced pressure to afford crude 7-hydroxychroman-4-one (164 g, 100% crude yield) as brown gum.

*Step 3: 7-(benzyloxy)chroman-4-one*

**[0285]** To a solution of 7-hydroxychroman-4-one (164 g, 1.0 mol, 1.0 eq) in ACN (1.50 L) was added $K_2CO_3$ (276 g, 2.0 mol, 2.0 eq) and benzylbromide (190 g, 1.1 mol, 1.1 eq) slowly. The mixture was stirred at 25° C for 12 hours, then poured into $H_2O$ (3 L), and extracted with EtOAc (2 x 1 L). The combined organic layer was washed with brine (2 L), dried over $Na_2SO_4$, filtered and concentrated in vacuum. The residue was purified by column chromatography on silica gel using 0-15% EtOAc/hexane to afford 7-(benzyloxy)chroman-4-one (185 g, 73% yield) as a yellow solid.

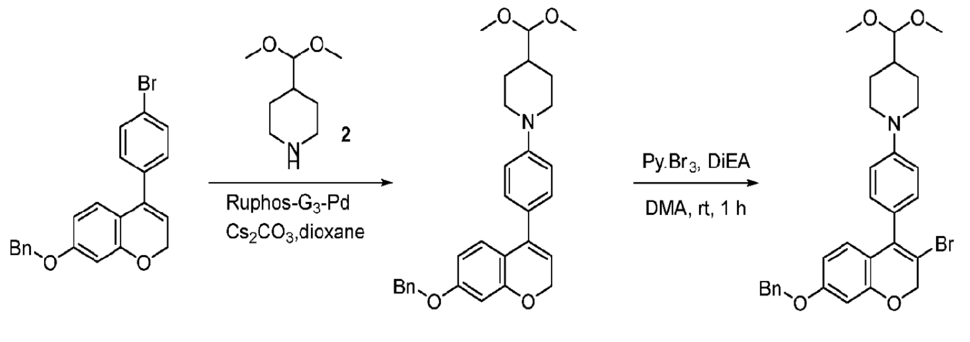
*Step 4: 7-(benzyloxy)-4-(4-bromophenyl) chroman-4-ol*

**[0286]** To a mixture of 1,4-dibromobenzene (5.1 g, 21.7 mmol, 1.1 eq) in dry THF (15 mL) was added n-BuLi (1.6 M, 25.6 mL, 1.30 eq) dropwise and the mixture was stirred at -78°C for 1 h. Then a solution of 7-(benzyloxy)chroman-4-one (5 g, 19.7 mmol, 1.0 eq) in THF (15 mL) was added and the mixture was stirred at -78°C for 1 h. The reaction was quenched with $NH_4Cl$ solution (30 mL), extracted with EtOAc (2 x 20 mL). 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 silica gel column chromatography using 0-30% EtOAc/hexane to afford 7-(benzyloxy)-4-(4-bromophenyl) chroman-4-ol (4.2 g, 52% yield) as a white solid.

*Step 5: 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene*

**[0287]** To a solution of 7-(benzyloxy)-4-(4-bromophenyl)chroman-4-ol (4.2 g, 10.2 mmol, 1.0 eq) in MeOH (20 mL) was added TsOH (39 mg, 0.2 mmol, 0.02 eq) and the mixture was stirred at 70 °C for 30 min and the mixture was concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-20% EtOAc/hexane to afford 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene (3.7 g, 92% yield) as a yellow gum. LC-MS purity: 96.9% (UV at 254 nm),392.9 $[M+H]^+$.

**Intermediate 2: 1-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine**




1 3 I-2

*Step 1: 1-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine*

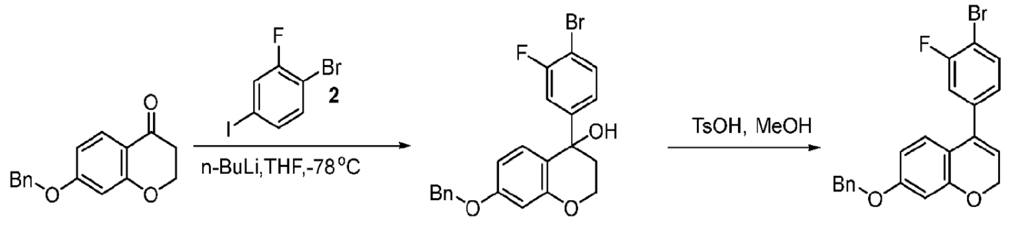
**[0288]** To a mixture of 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene (5.3 g, 13.5 mmol, 1 eq.), 4-(dimethoxymethyl)piperidine (2.36 g, 14.8 mmol, 1.05 eq.), $RuphosPdG_3$ (1.13 g, 1.35 mmol, 0.1 eq.), $CS_2CO_3$ (8.79 g, 27 mmol, 2 eq.) in dioxane (50 mL). The mixture was purged with $N_2$ and heated to 100 °C for 16 h. LCMS showed reaction was complete. The mixture was poured into

$H_2O$ (30 mL), extracted with EtOAc (20 mLx2), and the 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 1-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine (4.7 g, 73.9% yield) as a yellow solid. LC-MS purity: 98% (UV at 254 nm), 472.0 $[M+H]^+$

*Step 2: 1-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine*

**[0289]** To a solution of 1-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine (850 mg, 1.8 mmol, 1.00 eq.) and DIEA (465 mg, 3.6 mmol, 2.00 eq.) in DMA (5 mL), was added pyridinium tribromide (634 mg, 1.98 mmol, 1.1 eq.) at 0°C, and the mixture was stirred at 25° C for 1 h. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture was poured into $H_2O$ (30 mL), extracted with EtOAc (20 mLx2), and the 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 using 0-20% EtOAc/hexane to afford 1-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine (560 mg, 56.6% yield) as a yellow solid. LC-MS purity: 47% (UV at 254 nm), 551.9 $[M+H]^+$

**Intermediate 3: 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)-2H-chromene**




1 3 I-3

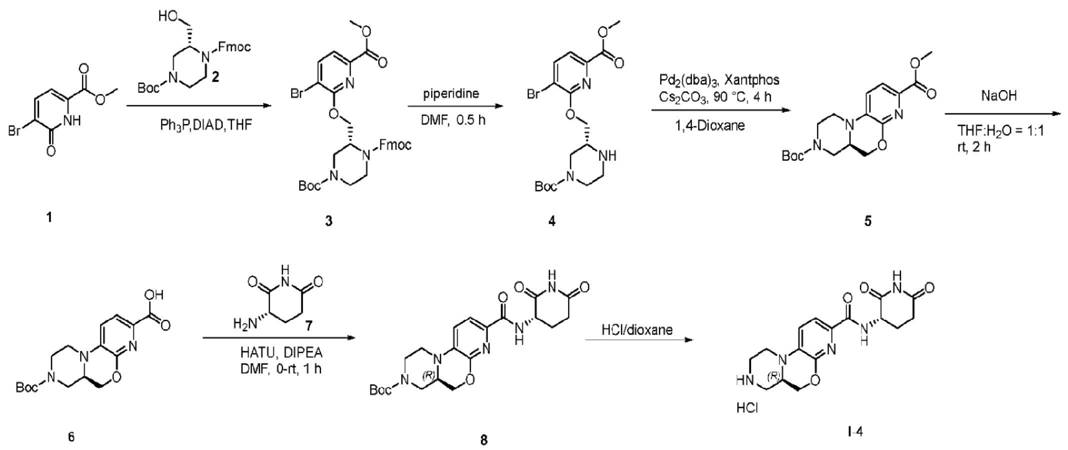
*Step 1: 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)chroman-4-ol*

**[0290]** To a mixture of 1-bromo-2-fluoro-4-iodobenzene (6.6 g, 22.0 mmol, 1.1 eq) in dry THF (15 mL) was added n-BuLi (1.6 M, 25.6 mL, 1.30 eq) dropwise and the mixture was stirred at -78°C for 1 h. Then a solution of 7-(benzyloxy)chroman-4-one (5 g, 19.7 mmol, 1.0 eq) in THF (15 mL) was added and the mixture was stirred at -78°C for 1 h. The reaction was quenched with $NH_4Cl$ solution (30 mL), extracted with EtOAc (2 x 20 mL), and 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 silica gel column chromatography using 0-30% EtOAc/hexane to afford 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)chroman-4-ol (4.3 g, 50% yield) as a white solid.

*Step 2: 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)-2H-chromene*

**[0291]** To a solution of 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)chroman-4-ol (4.3 g, 10.0 mmol, 1.0 eq) in MeOH (20 mL) was added TsOH (39 mg, 0.2 mmol, 0.02 eq) and the mixture was stirred at 70 °C for 30 min and the mixture was concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-20% EtOAc/hexane to afford 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)-2H-chromene (3.6 g, 90% yield) as a yellow gum. LC-MS purity: 47% (UV at 254 nm), 392.9 $[M+H]^+$.

**Intermediate 4: (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*

**[0292]** 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.) was warmed to 60 °C under Ar. To the mixture was added DIAD (6.5 g, 32.1 mmol, 3 eq.) dropwise and the mixture was stirred at 60 °C for 2 hours. 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 a yellow solid.

*Step 2: (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate*

**[0293]** 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 0.5 hour, 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 residue was purified by column chromatography on silica gel eluted with 0-5% DCM in methanol to afford (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), 430.2 $[M+H]^+$.

*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*

**[0294]** 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.) and the mixture was stirred at 90 °C for 4 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, 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 (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 a 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*

**[0295]** 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 hours. 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 a 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*

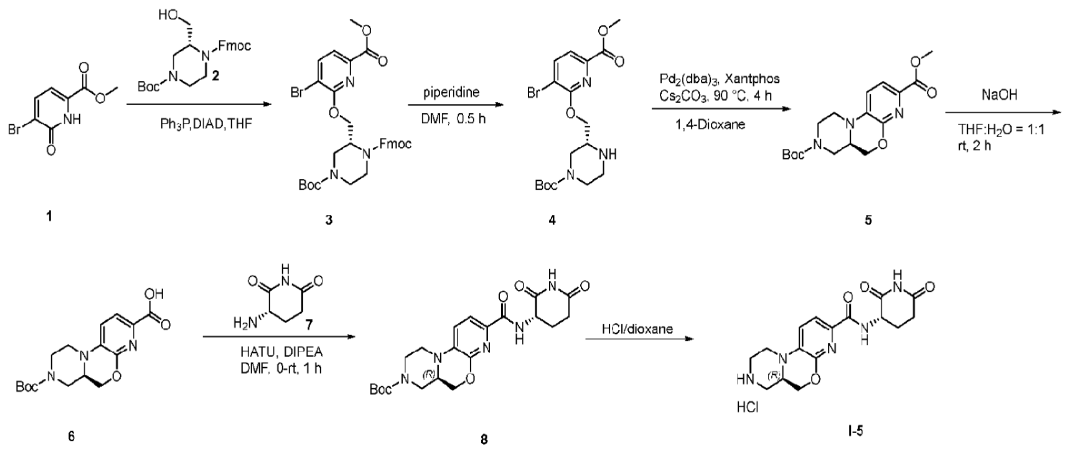
**[0296]** To a mixture of (R)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid (1.3 g, 3.8 mmol, 1 eq.) and (S)-3-aminopiperidine-2,6-dione (580 mg， 4.6 mmol， 1.2 eq ) in DMF (10 mL) was added HATU (1.7 g, 4.6 mmol, 1.2 eq.) and DIPEA (980 mg, 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*

**[0297]** 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. LC-MS purity: 100% (UV at 254 nm), 346.2[M+H]$^+$.

**[0298]** $^1$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 5: (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: (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate*

**[0299]** 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.) was warmed to 60 °C under Ar. To the mixture was added DIAD (6.5 g, 32.1 mmol, 3 eq.) dropwise and the mixture was stirred at 60 °C for 2 hours. 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 a yellow solid.

*Step 2: (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate*

**[0300]** 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 0.5 hour, 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 residue was purified by column chromatography on silica gel eluted with 0-5% DCM in methanol to afford (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), 430.2 $[M+H]^+$.

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

**[0301]** 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.) and the mixture was stirred at 90 °C for 4 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, 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 (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 a 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*

**[0302]** 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 hours. 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 a 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*

**[0303]** 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.) and (S)-3-aminopiperidine-2,6-dione (580 mg，4.6 mmol，1.2 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-

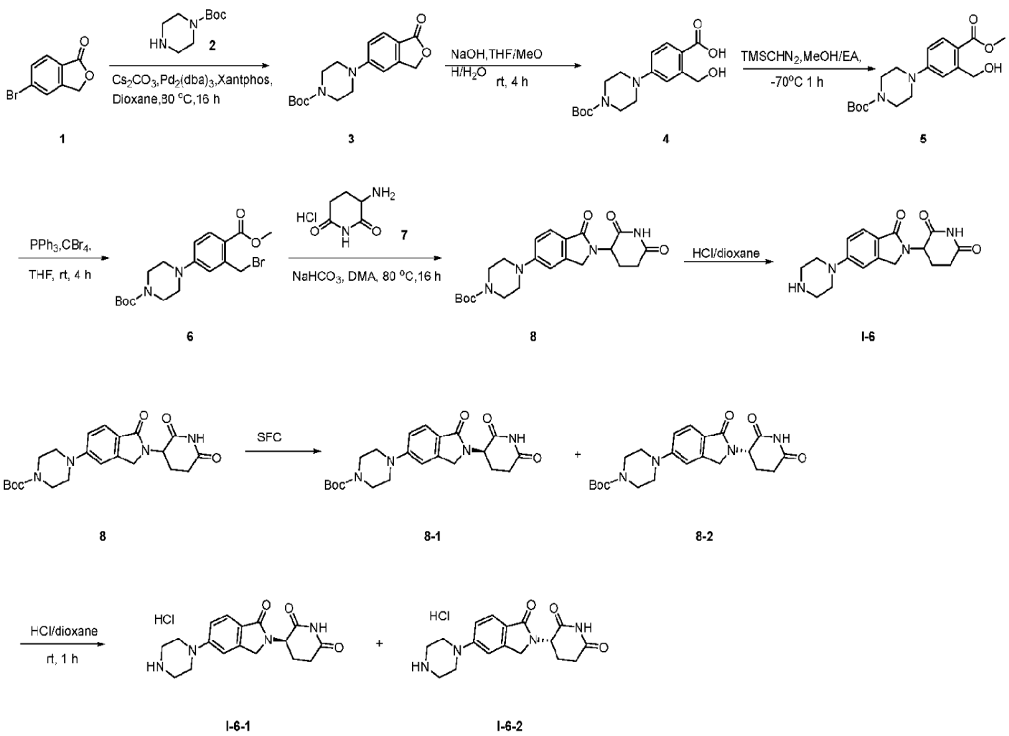
yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate (1.3 g , 76 % yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 446.2[M+H]$^+$.

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

**[0304]** 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. LC-MS purity: 100% (UV at 254 nm), 346.2[M+H]$^+$.

**[0305]** $^1$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 6: 3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt**



*Step 1: tert-butyl 4-(1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate*

**[0306]** To a mixture of 5-bromoisobenzofuran-1(3H)-one (10.0 g, 46.95 mmol, 1.0 eq) and tert-butyl piperazine-1-carboxylate in 1,4-dioxane (100 mL) was added $Cs_2CO_3$ (30.6 g, 93.90 mmol, 2.0 eq) and Xantphos (2.8 g, 4.70 mmol, 0.1 eq) followed by the addition of $Pd_2(dba)_3$ (2.2 g, 2.347 mmol, 0.05 eq.). The mixture was stirred at 80 °C for 12 hours under $N_2$ protection. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by column chromatography on silica gel (0-20% of EtOAc in PE) to afford tert-butyl 4-(1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate (6.50 g, 63.3%) as a yellow solid. LC-MS purity: 100 % (UV at 254 nm), 319.2 $[M+H]^+$.

*Step 2: 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(hydroxymethyl)benzoic acid*

**[0307]** To a mixture of tert-butyl 4-(1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate (6.5 g, 20.38 mmol, 1.0 eq) in MeOH (15 mL)/THF (15 mL)/$H_2O$ (15 mL) was added NaOH (3.7 g, 81.51 mmol, 4.0 eq). stirred at room temperature for 4 hours. The resulting mixture was dilute with water, adjusted to pH 5~6 with 1N HCl filtered. The solid was dried to afford 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(hydroxymethyl)benzoic acid (7.10 g, crude) as a white solid. LC-MS purity: 100 % (UV at 254 nm), 337.1 $[M+H]^+$.

*Step 3: tert-butyl 4-(3-(hydroxymethyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate*

**[0308]** To a mixture of 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(hydroxymethyl)benzoic acid (7.1 g, 21.131 mmol, 1.0 eq) in EtOAc (35 mL)/MeOH (35 mL) was dropwise $TMSCHN_2$ (2 M in n-Hexane, 27 mL) at -70°C and the mixture stirred for 1 hour under $N_2$ protection. The resulting mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (0-20% of EtOAc in PE) to afford tert-butyl 4-(3-(hydroxymethyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (7.8 g, crude) as yellow oil. LC-MS purity: 100 % (UV at 254 nm), 351.3 $[M+H]^+$.

*Step 4: tert-butyl 4-(3-(bromomethyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate*

**[0309]** To a mixture of tert-butyl 4-(3-(hydroxymethyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (7.8 g, 22.222 mmol, 1.0 eq) in THF (70 mL) was added $PPh_3$ (8.8 g, 33.333 mmol, 1.5 eq), $CBr_4$ (11.1 g, 33.333 mmol, 1.5 eq). The resulting was stirred at room temperature for 4 hours, concentrated. The residue was purified by silica gel chromatography column chromatography on silica gel (0-20% of EtOAc in PE) to afford tert-butyl 4-(3-(bromomethyl)-4-

(methoxycarbonyl)phenyl)piperazine-1-carboxylate (6.8 g, 73.9% yield) as a yellow solid. LC-MS purity: 100 % (UV at 254 nm), 414.9 $[M+H]^+$.

*Step 5: tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate*

**[0310]** To a mixture of tert-butyl 4-(3-(bromomethyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (3.4 g, 8.226 mmol, 1.0 eq.), 3-aminopiperidine-2,6-dione hydrochloride (4.1 g, 24.679 mmol, 3.0 eq.) in DMA (20 mL) was added $NaHCO_3$ (2.1 g, 24.679 mmol, 3.0 eq.) and the mixture stirred at 80 °C for 16 hours. The resulting mixture was purified by reverse flash chromatography, with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 0% to 100% gradient in 20 min; detector, UV 254 nm to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate (1.5 g, 43.0% yield) as a blue solid. LC-MS purity: 100 % (UV at 254 nm), 429.0 $[M+H]^+$.

**[0311]** 1H NMR (400 MHz, DMSO): δ 10.93 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.12 – 7.01 (m, 2H), 5.05 (dd, J = 13.2, 5.2 Hz, 1H), 4.27 (dd, J = 49.2, 16.8 Hz, 2H), 3.48 – 3.44 (m, 3H), 3.32 – 3.25 (m, 5H), 2.96 – 2.84 (m, 1H), 2.62 – 2.55 (m, 1H), 2.43 – 2.31 (m, 1H), 2.00 – 1.92 (m, 1H), 1.42 (s, 9H).

*Step 6: 3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt*

**[0312]** A mixture of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate (100 mg) in HCl/dioxane (2 mL) was stirred at rt for 1 hour. Then the solution was concentrated to afford 3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt as light-blue solid (90 mg, crude, ca. 100% yield). LC-MS purity: 100 % (UV at 254 nm), 329.0 $[M+H]^+$.

*Step 7: SFC separation of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate*

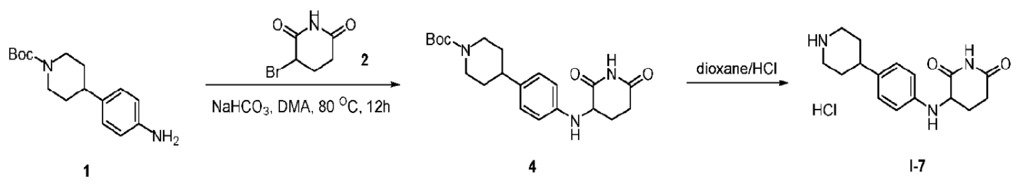
**[0313]** tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate(500 mg) was separated via SFC to afford (R)-tert-butyl-4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate and (S)-tert-butyl-4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate(isomer 1:240 mg, isomer 2: 220 mg) .

| | |
|---|---|
| **System：** | Waters SFC 150 |
| **Column name:** | DAICELCHIRALPAK®AD |
| **Column size：** | 250*25 mm 10 μm |
| **Mobile Phase A：** | Supercritical $CO_2$, |
| **Mobile Phase B：** | MEOH (+0.1% 7.0mol/l Ammonia in MEOH) |
| **A:B:** | 75:25 |
| **Wavelength：** | 214 nm |
| **Flow:** | 70ml/min |
| **Column temp:** | RT |
| **Back Pressure:** | 100 bar |
| **Injection:** | 1mL |
| **Cycle time:** | 3.8min |
| **Solvent:** | MeOH: redistilled grade<br>Supercritical $CO_2$: Food grade |

*Step 8: (R)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt or (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt*

**[0314]** A mixture of (R)-tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate or (s)-tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate (100 mg) in HCl/dioxane (2 mL) was stirred at rt for 1 hour. Then the solution was concentrated to afford (R)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt or (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt (90 mg, 100% crude yield) as a light-blue solid. LC-MS purity: 100 % (UV at 254 nm), 329.0 $[M+H]^+$.

**Intermediate 7: 3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt**



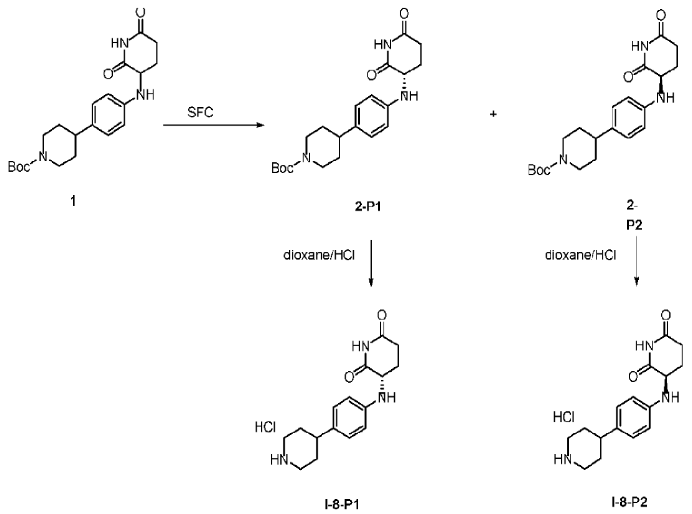

*Step 1: tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate*

**[0315]** 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 for 12 hours 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 (1.6 g, 76.0 % yield) as a light blue solid. 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*

**[0316]** 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 hydrochloride (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 8: Two single isomers of 3-((4-(piperidin-4-yl)phenyl)amino) piperidine-2,6-dione hydrochloride salt (structures were tentatively assigned)**




*Step 1: Two single isomers of tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate*

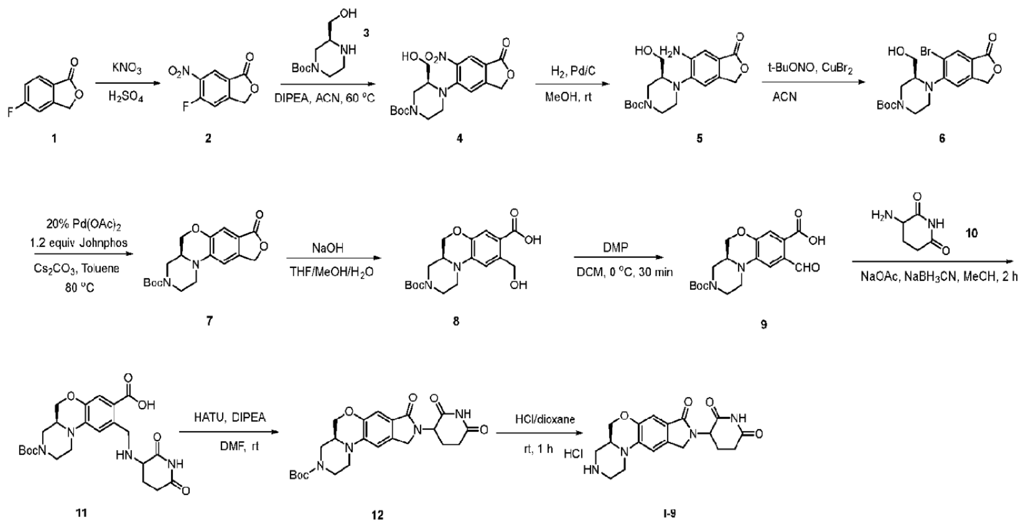
**[0317]** tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate (1.9 g, 5 mmol) was purified via SFC as method below to afford two single isomers (P1:450 mg, P2: 480 mg), LC-MS purity: 100% (UV at 254 nm), 388.0 $[M+H]^+$.

| | |
|---|---|
| **System：** | Waters SFC 150 |
| **Column name:** | DAICELCHIRALPAK®AS |
| **Column size：** | 250*25 mm 10 μm |
| **Mobile Phase A：** | Supercritical $CO_2$, |
| **Mobile Phase B：** | MEOH (+0.1% 7.0mol/l Ammonia in MEOH) |
| **A:B:** | 75:25 |
| **Wavelength：** | 214 nm |
| **Flow:** | 70ml/min |
| **Column temp:** | RT |
| **Back Pressure:** | 100 bar |
| **Injection:** | 1mL |
| **Cycle time:** | 3.8min |
| **Solvent:** | MeOH: redistilled grade<br>Supercritical $CO_2$: Food grade |

*Step 2: Two single isomers of 3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt*

**[0318]** A mixture of (S)-tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate or (R)-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 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**



*Step 1: 5-fluoro-6-nitroisobenzofuran-1(3H)-one*

**[0319]** 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, then slowly poured into ice water (100 mL) and extracted with EtOAc (100 mL x 3). 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 (10.4 g, 80% yield) as a white solid.

*Step 2: tert-butyl (S)-3-(hydroxymethyl)-4-(6-nitro-1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate*

**[0320]** 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 (1.3 g, 66% yield) as yellow foam. LC-MS purity: 77.1% (UV at 254 nm), 394.0 $[M+H]^+$.

*Step 3: tert-butyl (S)-4-(6-amino-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate*

**[0321]** 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 (860 mg, 93% yield) as light yellow foam. LC-MS purity: 95.7% (UV at 254 nm), 364.1 $[M+H]^+$

*Step 4: tert-butyl (S)-4-(6-bromo-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate*

**[0322]** To a solution of 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) was added *t*-BuONO (0.2 mL, 1.7 mmol, 1.3 eq.) under ice bath 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 (415 mg, 75% yield ) as brown oil. LC-MS purity: 46% (UV at 254 nm), 427.1, 429.1 $[M+H]^+$.

*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*

**[0323]** 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 80 °C for 3 h. The mixture 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 (90 mg, 80% yield) as a yellow solid. LC-MS purity: 45.5% (UV at 254 nm), 347.1 $[M+H]^+$.

*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*

**[0324]** 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 (76 mg , 83% yield) as a white solid. LC-MS purity: 68.9% (UV at 254 nm), ms: 347.0 $[M+H-18]^+$.

*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*

**[0325]** 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 (20 mL) 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 (50 mg, crude) as a yellow solid.

*Step 8: (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*

**[0326]** 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.) in MeOH (6 mL) was added $NaBH_3CN$ (36 mg, 0.6 mmol, 3 eq.) and the mixture was stirred at room temperature for 2 h. Then the reaction was quenched with water (5 mL) 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 (35 mg, 38% yield) as a white solid. LC-MS purity: 65.6% (UV at 254 nm), 475.2 $[M+H]^+$.

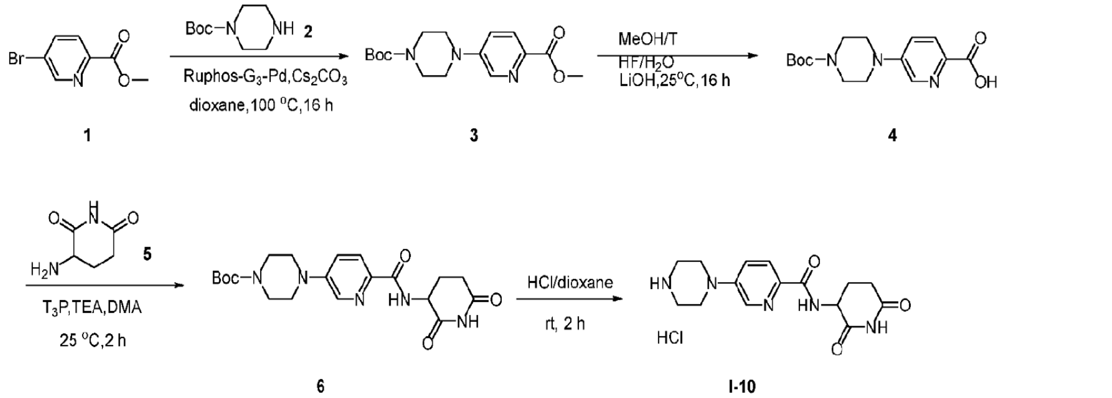
*Step 9: tert-butyl (4aS)-9-(2,6-dioxopiperidin-3-yl)-8-oxo-1,2,4a,5,9,10-hexahydro-8H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindole-3(4H)-carboxylate*

**[0327]** 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 (2.5 mL) 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 a white solid. LC-MS purity: 100% (UV at 254 nm), 457.2 $[M+H]^+$.

*Step 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*

**[0328]** 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 1 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 hydrochloride salt (26 mg, crude) as a white solid. LC-MS purity: 100% (UV at 254 nm), 357.2 $[M+H]^+$

**Intermediate 10: 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*

**[0329]** 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.). The mixture was stirred at 100 °C for 16 h under Ar and then cooled to room temperature, concentrated. 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). LC-MS purity: 76.1% (UV at 254 nm), 322.4 $[M+H]^+$.

*Step 2: 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)picolinic acid*

**[0330]** 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 to remove THF and then 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). LC-MS purity: 79.5% (UV at 254 nm), 308.1 $[M+H]^+$.

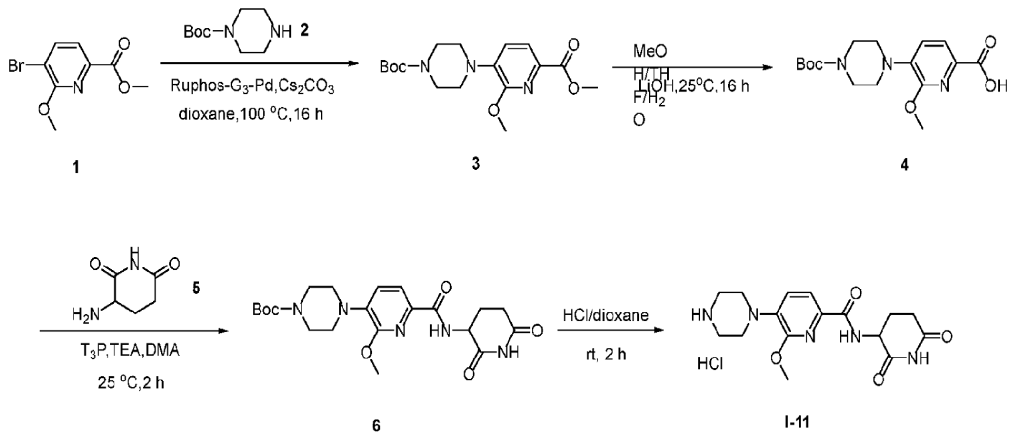
*Step 3: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)pyridin-3-yl)piperazine-1-carboxylate*

**[0331]** 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 a white solid. LC-MS purity: 100% (UV at 254 nm), 418.4 $[M+H]^+$.

*Step 4: N-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)picolinamide hydrochloride salt*

**[0332]** 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 (950 mg, crude) as a white solid. LC-MS purity: 100% (UV at 254 nm), 318.1 $[M+H]^+$

**Intermediate 11: 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*

**[0333]** 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.). The mixture was stirred at 100 °C for 16 h under Ar and then 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%). LC-MS purity: 39% (UV at 254 nm), 352.2 $[M+H]^+$

*Step 2: 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-methoxypicolinic acid*

**[0334]** 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 to remove MeOH and THF 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). LC-MS purity: 100% (UV at 254 nm), 338.1 $[M+H]^+$

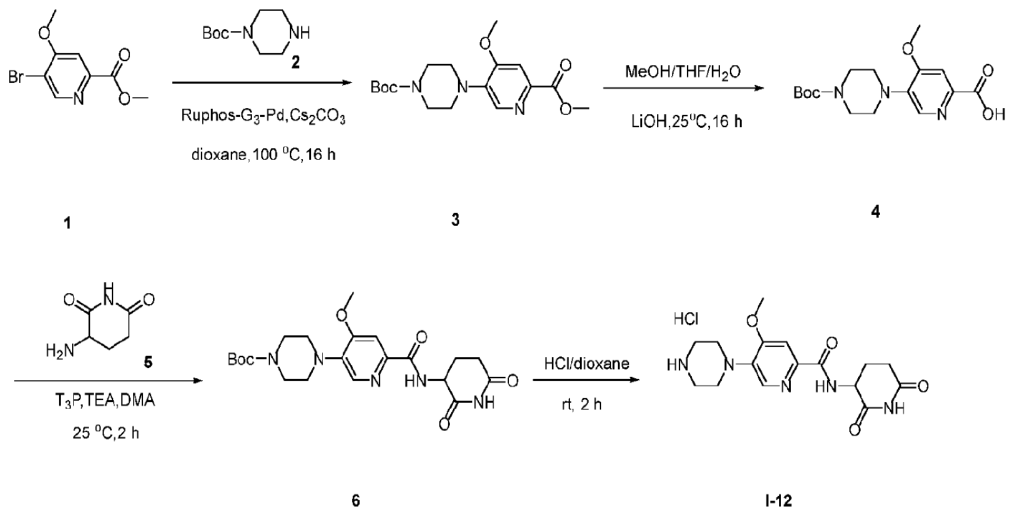
*Step 3: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methoxypyridin-3-yl)piperazine-1-carboxylate*

**[0335]** 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, then 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 a white solid. LC-MS purity: 100% (UV at 254 nm), 448.1 $[M+H]^+$.

*Step 4: N-(2,6-dioxopiperidin-3-yl)-6-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride salt*

**[0336]** 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). 100% (UV at 254 nm), 348.1 $[M+H]^+$.

**Intermediate 12: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)pyridin-3-yl)piperazine-1-carboxylate.**




*Step 1: tert-butyl 4-(4-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate*

**[0337]** To a mixture of methyl 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). LC-MS purity: 25.3% (UV at 254 nm), 352.2 $[M+H]^+$.

*Step 2: 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-methoxypicolinic acid*

**[0338]** 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). LC-MS purity: 100% (UV at 254 nm), 338.1 $[M+H]^+$

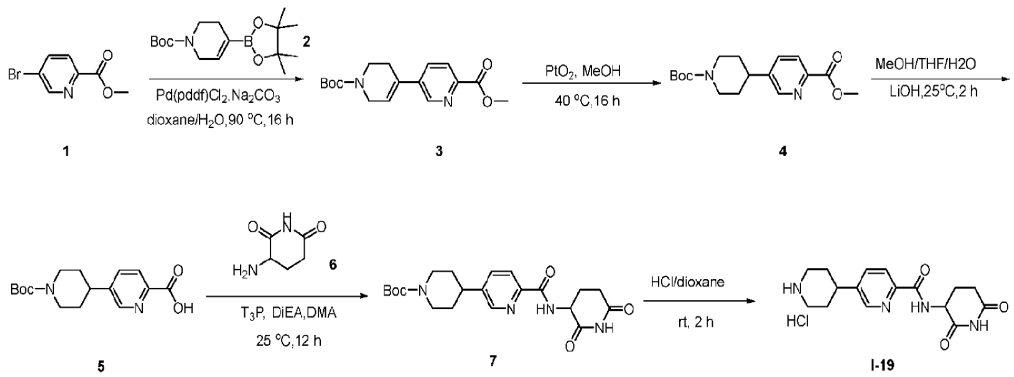
*Step 3: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-4-methoxypyridin-3-yl)piperazine-1-carboxylate*

**[0339]** 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 a white solid. LC-MS purity: 100% (UV at 254 nm), 448.1 $[M+H]^+$.

*Step 4: N-(2,6-dioxopiperidin-3-yl)-4-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride salt*

**[0340]** 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). LC-MS purity: 100% (UV at 254 nm), 348.1 $[M+H]^+$.

**Intermediate 13: N-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)picolinamide hydrochloride salt**



*Step 1: 1'-(tert-butyl) 6-methyl 3',6'-dihydro-[3,4'-bipyridine]-1',6(2'H)-dicarboxylate*

**[0341]** To a mixture of methyl 5-bromopicolinate (10 g, 46.2 mmol 1 eq.) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (15.7 g, 50.9 mmol, 1.1 eq.) in dioxane (100 mL)/$H_2O$ (20 ml) was added Pd(pddf)$Cl_2$ (2.1 g, 2.31 mmol, 0.05 eq.) and $Na_2CO_3$ (9.7 g, 92.4 mmol, 2 eq.). The reaction mixture was stirred at 90 °C under $N_2$ for 16 hours, concentrated. The residue was purified by column chromatography on silica gel eluted with 0-30% EtOAc/hexane to afford 1'-(tert-butyl) 6-methyl 3',6'-dihydro-[3,4'-bipyridine]-1',6(2'H)-dicarboxylate (15.1 g, 95% yield) as yellow oil. LC-MS purity: 100% (UV at 254 nm), 319.2 $[M+H]^+$.

*Step 2: methyl 5-(1-(tert-butoxycarbonyl) piperidin-4-yl) picolinate*

**[0342]** To a mixture of 1'-(tert-butyl) 6-methyl 3',6'-dihydro-[3,4'-bipyridine]-1',6(2'H)-dicarboxylate (15.1 g, 1 eq.) in MeOH (150ml) was added $PtO_2$ (680 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 methyl 5-(1-(tert-butoxycarbonyl) piperidin-4-yl) picolinate (15 g, crude). LC-MS purity: 100% (UV at 254 nm), ms: 321.2 $[M+l]^+$.

*Step 3: 5-(1-(tert-butoxycarbonyl) piperidin-4-yl) picolinic acid.*

**[0343]** To a mixture of methyl 5-(1-(tert-butoxycarbonyl) piperidin-4-yl)picolinate (3.2 g,10 mmol, 1 eq.) in MeOH (15 ml)/THF(15 ml)/$H_2O$(15 ml). The reaction mixture was stirred at room temperature for 2 hours. 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-(1-(tert-butoxycarbonyl) piperidin-4-yl) picolinic acid. LC-MS purity: 100% (UV at 254 nm), 307.0 $[M+H]^+$

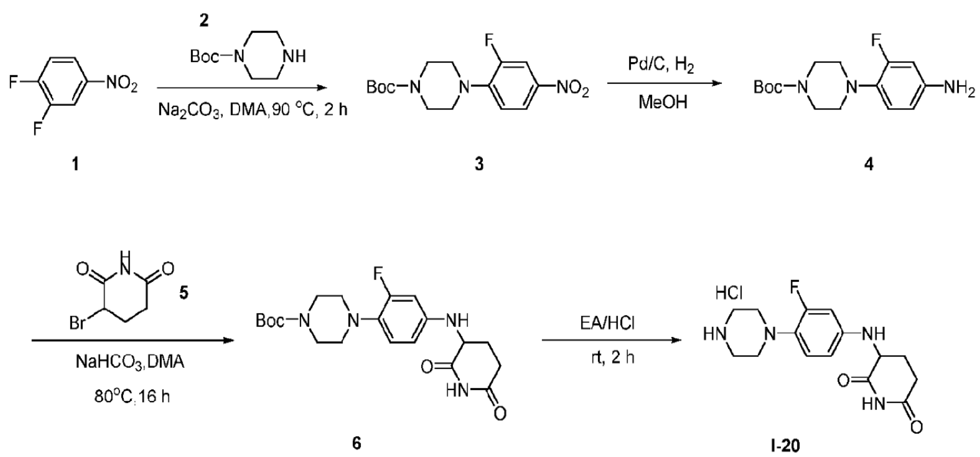
*Step 4: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl) carbamoyl)pyridin-3-yl)piperazine-1-carboxylate*

**[0344]** To a mixture of 5-(1-(tert-butoxycarbonyl)piperidin-4-yl)picolinic acid (500 mg, 1.6 mmol, 1 eq.) and 3-aminopiperidine-2,6-dione (204 mg, 1.9 mmol, 1.2 eq.) in DMA (20 ml) was added TEA (660 mg, 6.4 mmol, 4 eq.) and TBTU (786 mg, 10 mmol, 1.5 eq.). The mixture was stirred at room temperature for 12 h under $N_2$. The mixture 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 (360 mg, 70% yield ). LC-MS purity: 100% (UV at 254 nm), 417.2 $[M+H]^+$.

*Step 5: N-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yl)picolinamide hydrochloride salt*

**[0345]** A mixture of 4-(6-((2,6-dioxopiperidin-3-yl) carbamoyl)pyridin-3-yl)piperazine-1-carboxylate (100 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 N-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yl)picolinamide hydrochloride salt (90 mg, crude) as a white solid. LC-MS purity: 100% (UV at 254 nm), 317.2 $[M+H]^+$.

**Intermediate 14: 3-((4-(piperazin-1-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt**




*Step 1: tert-butyl 4-(2-fluoro-4-nitrophenyl)piperazine-1-carboxylate*

**[0346]** To a mixture of 1,2-difluoro-4-nitrobenzene (10 g, 62.9 mmol 1 eq.) and $KCO_3$ (17.4 g. 125.7 mmol, 2 eq.) in DMA (50 mL) was added tert-butyl piperazine-1-carboxylate (14.1 g, 75.4 mmol, 1.2 eq.) and the reaction mixture was stirred at 90°C for 2 h. The mixture was poured into ice water (500 mL) and stirred for 30 min. The precipitate was collected by filtration and dried in vacuo to afford tert-butyl 4-(2-fluoro-4-nitrophenyl)piperazine-1-carboxylate (20.4 g, crude) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 270.1 [M+H-56]$^+$.

*Step 2: tert-butyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate*

**[0347]** To a solution of tert-butyl 4-(2-fluoro-4-nitrophenyl)piperazine-1-carboxylate (3.2 g, 10 mmol, 1 eq.) in MeOH (50 mL) was added Pd/C (640 mg, 10% on Carbon, wetted with ca. 55% water ) and the reaction mixture was stirred at room temperature for 16 h. The catalyst was removed by filtration and the filtrate was concentrated to afford tert-butyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate (2.9 g, crude ) as a purple solid. LC-MS purity: 99.1% (UV at 254 nm), 296.1 [M+H]$^+$.

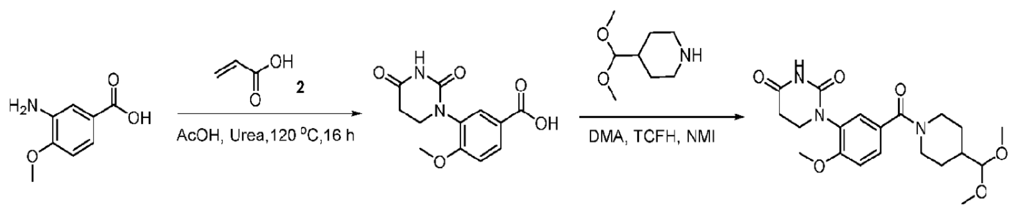
*Step 3: tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)-2-fluorophenyl)piperazine-1-carboxylate*

**[0348]** To a mixture of tert-butyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate (1.0 g, 3.4 mmol 1 eq.) and 3-bromopiperidine-2,6-dione (650 mg, 3.4 mmol, 1 eq.) in DMA (20 mL) was added $NaHCO_3$ (290 mg, 3.4 mmol, 1 eq.). The reaction mixture was stirred at 80 ºC for 16 h, cooled to room temperature and then poured into water (200 mL). The precipitate was collected by filtration and dried in vacuo to afford tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)-2-fluorophenyl)piperazine-1-carboxylate (860 mg, crude) as a green solid. LC-MS purity: 100% (UV at 254 nm), 407.2 [M+H]$^+$.

*Step 4: 3-((3-fluoro-4-(piperazin-1-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt*

**[0349]** A mixture of tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)-2-fluorophenyl)piperazine-1-carboxylate ( 860 mg, 2.8 mmol, 1 eq.) in EA/HCl (10 ml) was stirred at room temperature for 2 h. The mixture was concentrated to afford 3-((3-fluoro-4-(piperazin-1-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt (840 mg, crude ) as a blue solid. LC-MS purity: 100% (UV at 254 nm), 307.1 [M+H]$^+$.

**Intermediate 15: 4-(5-(4-(dimethoxymethyl)piperidine-1-carbonyl)-2-methoxyphenyl)piperazine-2,6-dione**

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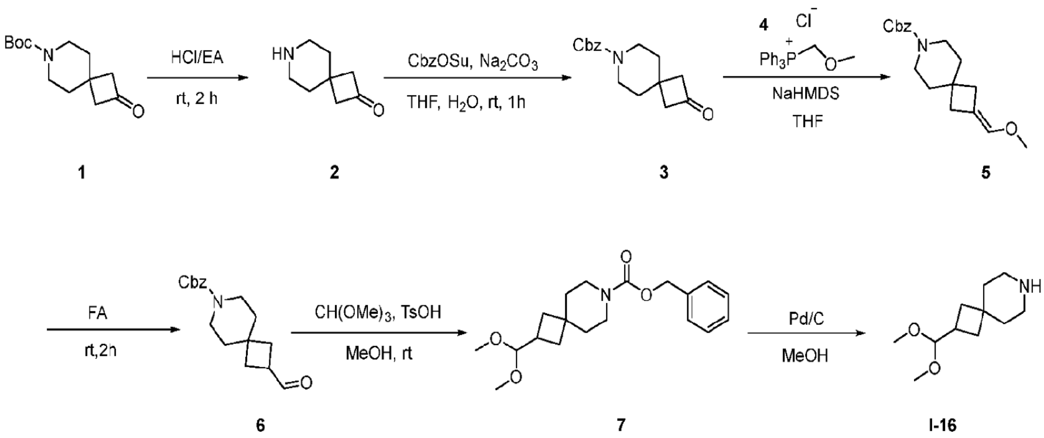
*Step 1: 3-(3,5-dioxopiperazin-1-yl)-4-methoxybenzoic acid*

**[0350]** To a mixture of methyl-3-amino-4-methoxybenzoic acid (3.0 g, 17.9 mmol, 1 eq.) and acrylic acid (4.8 ml, 72.1 mmol, 4 eq.) in AcOH (20 mL) was added urea (6.6 g). The reaction mixture was stirred at 120 °C for 16 hours and then cooled to room temperature. The mixture was poured into ice-water (100 mL). The precipitate was collected by filtration, dried in *vacuo* to afford 3-(3,5-dioxopiperazin-1-yl)-4-methoxybenzoic acid (3.8 g, crude) as a yellow solid. LC-MS purity: 59.4% (UV at 254 nm), 265.0 $[M+H]^+$.

*Step 2:*

**[0351]** To a mixture of 3-(3,5-dioxopiperazin-1-yl)-4-methoxybenzoic acid (150 mg, 0.566 mmol, 1 eq.) in DMA (1.5 ml) was added NMI (0.45 ml, 5.660 mmol 10 eq.) and TCFH (317 mg, 1.132 mmol, 2.0 eq.) and the mixture was stirred for 30min. Then to the mixture was added 4-(dimethoxymethyl) piperidine(108 mg, 0.679 mmol, 1.2 eq) and the resulting mixture was stirred at 25°C for 12 h. The mixture was purified by prep-HPLC to afford 4-(5-(4-(dimethoxymethyl)piperidine-1-carbonyl)-2-methoxyphenyl)piperazine-2,6-dione (180 mg) as a white solid. LC-MS: 265.0 $[M+H]^+$.

**Intermediate 16: 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane**




*Step 1: benzyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate*

**[0352]** To a stirred solution of tert-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (24 g, 0.1 mol, 1 eq.) in EtOAc (50 mL) was added conc. HCl (45 mL, 0.5 mol, 5 eq.) slowly at room temperature and the reaction mixture was stirred at room temperature for 2 hours. Then the mixture was diluted with EtOAc (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 hour. 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 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (27 g, 100% yield) as light yellow oil.

*Step 2: benzyl 2-(methoxymethylene)-7-azaspiro[3.5]nonane-7-carboxylate*

**[0353]** To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (68 g, 0.2 mol, 2 eq.) in dried THF (300 mL) cooled at -78 °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 hours. Then the mixture was cooled at -78 °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 room temperature slowly and stirred for 2 hours. 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 column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford compound benzyl 2-(methoxymethylene)-7-azaspiro[3.5]nonane-7-carboxylate (20 g, 67% yield) as light yellow oil.

*Step 3: benzyl 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate*

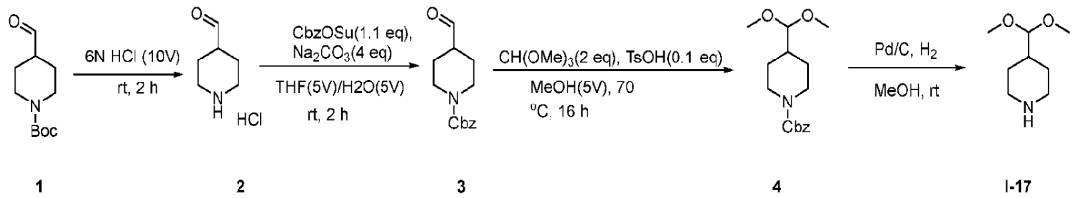
**[0354]** A solution of benzyl 2-(methoxymethylene)-7-azaspiro[3.5]nonane-7-carboxylate (24 g, 0.67 mol, 1 eq.) in HCOOH (50 mL) was stirred at room temperature for 2 hours. The mixture was concentrated, and the residue was dissolved in MeOH (120 mL). To the mixture was added $CH(OMe)_3$ (10.6 g, 0.1 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. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (14.6 g, 67% yield) as light yellow oil.

*Step 4: 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane*

**[0355]** To a solution of benzyl 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (14.6 g, 440 mmol, 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 room temperature for 12 h under $H_2$ (1 atm). The catalyst was removed by filtration and the filtrate was concentrated to afford 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (8.9 g, ca.100%) as a white solid.

**[0356]** $^1$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 17: 4-(dimethoxymethyl)piperidine**




*Step 1: benzyl 4-formylpiperidine-1-carboxylate*

**[0357]** To a stirred solution of 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 room temperature for 2 hours. 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 stirred for 20 min. To the mixture was added CbzOSu (550 g, 2.2 mmol, 1 eq.) and the mixture was stirred for 2 hours. 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 4-formylpiperidine-1-carboxylate (550 g, 95% yield) as light yellow oil.

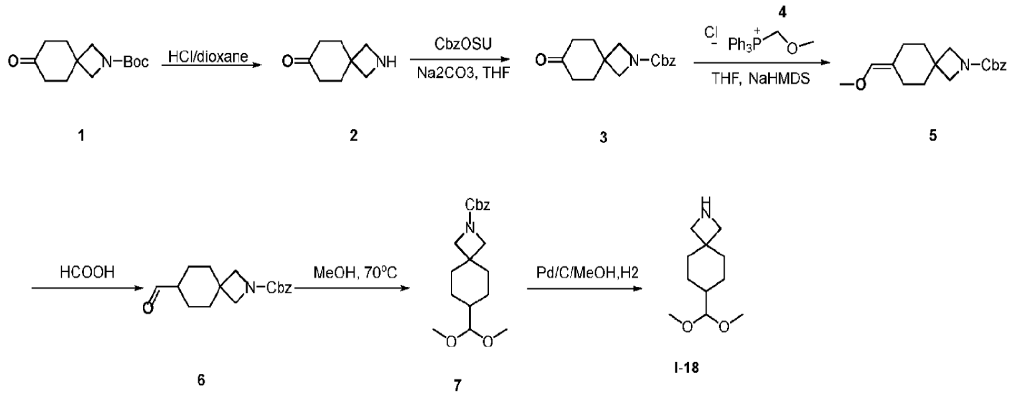
*Step 2: benzyl 4-(dimethoxymethyl)piperidine-1-carboxylate*

**[0358]** 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 16 hours. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-20% EtOAc/hexane to afford benzyl 4-(dimethoxymethyl)piperidine-1-carboxylate (120 g, , 82% yield) as light yellow oil.

*Step 3: 4-(dimethoxymethyl)piperidine*

**[0359]** To a solution of 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 room temperature for 12 h under $H_2$ (1 atm). The catalyst was removed by filtration and the filtrate was concentrated to afford 4-(dimethoxymethyl)piperidine (65 g, crude) as a white solid.

**Intermediate 18: 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane**




*Step 1: benzyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate*

**[0360]** To a stirred solution of tert-butyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate (12 g, 50 mmol, 1 eq.) in EA (30 mL) at room temperature was added conc. HCl (20 mL, 0.25 mol, 5 eq.) slowly and the reaction mixture was stirred at room temperature for 1 h. Then the mixture was diluted with EtOAc (70 mL), poured into $Na_2CO_3$ suspension (53 g, 0.5 mol, 10 eq., in 500 mL of water) and the mixture was stirred for 20 min. To the mixture was added CbzOSu (12.5 g, 50 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-2-azaspiro[3.5]nonane-2-carboxylate (13 g, 96% yield) as light yellow oil.

*Step 2: benzyl 2-(methoxymethylene)-7-azaspiro[3.5]nonane-7-carboxylate*

**[0361]** To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (34 g, 0.1 mol, 2 eq.) in dried THF (300 mL) cooled at -70 °C was added NaHMDS (50 mL, 0.1 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 (13 g, 50 mmol, 1eq.) in THF (50 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 EtOAc (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 7-(methoxymethylene)-2-azaspiro[3.5]nonane-2-carboxylate (9.1 g, mmol, 61% yield) as light yellow oil.

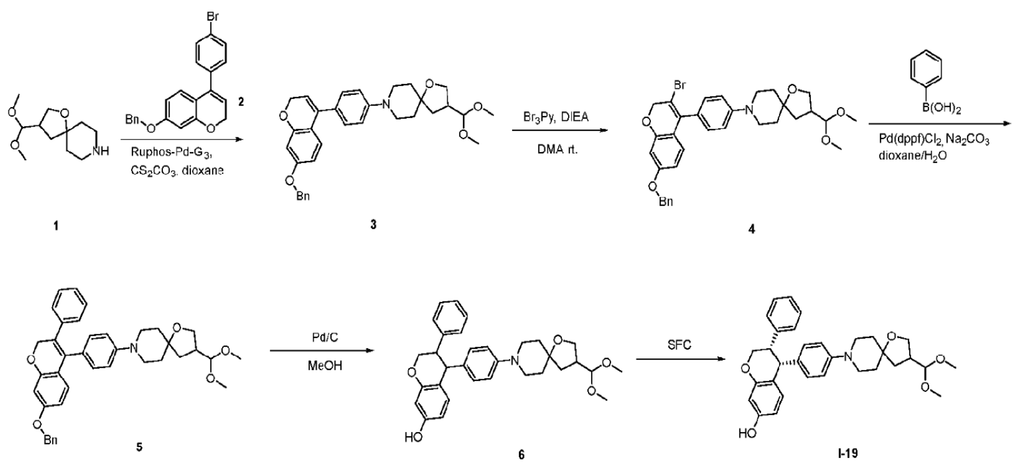
*Step 3: benzyl 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate*

**[0362]** A solution of benzyl 7-(methoxymethylene)-2-azaspiro[3.5]nonane-2-carboxylate (9.1 g, 61 mmol, 1 eq.) in Formic acid (20 mL) was stirred at room temperature for 4 h. The mixture was concentrated, and the residue was dissolved in MeOH (120 mL). To the mixture was added $CH(OMe)_3$ (9.1 g, 90 mmol, 1.5 eq.) followed by $TsOH{\cdot}H_2O$ (1.1 g, 0.06 mol, 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)-2-azaspiro[3.5]nonane-2-carboxylate (8 g, 40% yield) as light yellow oil.

*Step 4: 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane*

**[0363]** To a solution of benzyl 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate (8 g, 24mmol, 1 eq.) in MeOH (50 mL) was added Pd/C (2 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 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane (4.8 g, crude, ca. 100% yield) as a white solid.

**Intermediate 19: (3S,4R)-4-(4-(3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)phenyl)-3-phenylchroman-7-ol**




*Step 1: 8-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane*

**[0364]** To a solution of 3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (1.28 g, 5.95 mmol, 1.00 eq) in dioxane (15 mL) was added Ruphos-Pd-G3 (500 mg, 0.6 mmol, 0.1 eq), $Cs_2CO_3$ (3.88 g, 12 mmol, 2 eq), 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene (2.33 g, 5.95 mmol, 1 eq) and the mixture was stirred at 100 °C for 12 hours. The mixture concentrated in vacuum. The crude product was purified by column chromatography on silica gel using 0-20% EtOAc/hexane to afford 8-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (2.1 g, 70.5% yield) as yellow solid.

*Step 2: 8-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane*

**[0365]** To a solution of 8-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (2.1 g, 3.98 mmol, 1 eq.) and DIEA (1.0 g, 7.97 mmol, 2.00 eq) in DMA (10 mL) was added pyridinium tribromide (1.5 g, 4.8 mmol, 1.2 eq.) at 0° C, and the mixture was stirred at room temperature for 1 hour. The mixture was poured into $H_2O$ (30 mL), extracted with EtOAc (20 mL x 2). The 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 using 0-20% EtOAc/hexane to afford 8-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (2.2 g, 91.36% yield) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 606.3$[M+H]^+$.

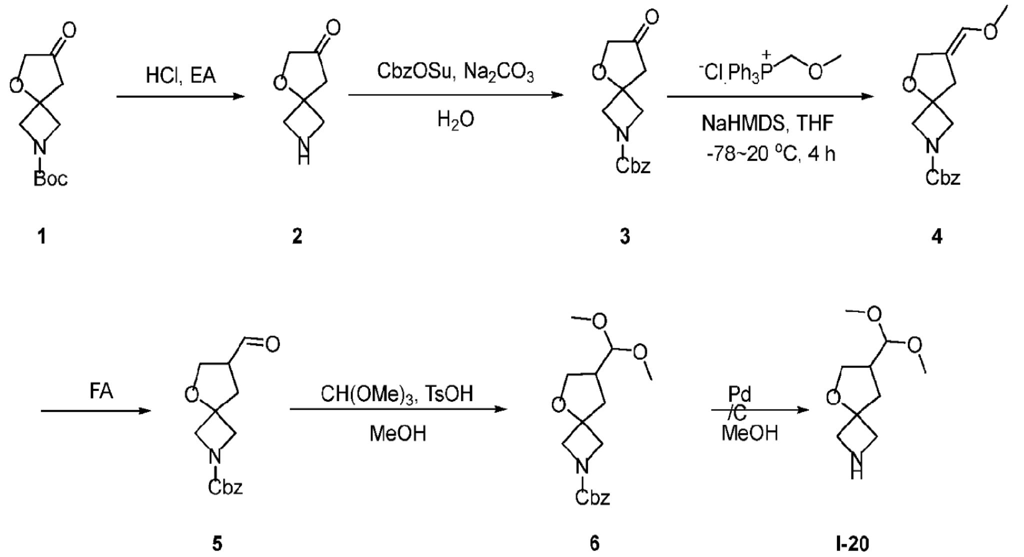
*Steps 3: 8-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane*

**[0366]** To a mixture of 8-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (2.2 g, 3.64 mmol, 1.00 eq) in dioxane (10 mL) and $H_2O$ (2 mL) was added $Na_2CO_3$ (1.16 g, 10.92 mmol, 3.00 eq) and Pd(dppf)$Cl_2$ (330 mg, 0.36 mmol, 0.1 eq), phenylboronic acid (0.53 g, 4.36 mmol, 1.20 eq) and the mixture was stirred at 100°C for 12 hours under Ar. The mixture was poured into $H_2O$ (50 mL), extracted with EtOAc (20 mL x 2). 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 eluted with 0-30% EtOAc/hexane to afford 8-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (1.4 g, 63.8%) as yellow solid. LC-MS purity: 100% (UV at 254 nm), 604.5$[M+H]^+$.

*Steps 4: 4-(4-(3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)phenyl)-3-phenylchroman-7-ol*

**[0367]** To a solution of 8-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (1.4 g, 2.32 mmol, 1.00 eq) in MeOH (10 mL) was added Pd/C (100 mg, 10% on carbon, wetted with c.a.55% water) and the mixture stirred at room temperature overnight under $H_2$. The mixture was filtered, and the filtrate was concentrated in vacuum to afford 4-(4-(3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)phenyl)-3-phenylchroman-7-ol (1.01 g, 84.53 % yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), 516.4 $[M+H]^+$.

**Intermediate 20: (3S,4R)-4-(4-(3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)phenyl)-3-phenylchroman-7-ol**




*Step 1: benzyl 7-oxo-5-oxa-2-azaspiro[3.4]octane-2-carboxylate*

**[0368]** 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 EtOAc (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 hour. 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*

**[0369]** To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (28.3 g, 80 mmol, 2 eq.) in dried THF (300 mL) cooled at -78 °C was added NaHMDS (40 mL, 160 mmol, 2 eq.)

dropwise and the mixture was warmed to 0 °C slowly and stirred for 2 hours. Then the mixture was cooled at -78 °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 hours. The mixture was quenched by $NH_4Cl$ solution (200 mL) and diluted with EtOAc (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, 40% yield) as light yellow oil.

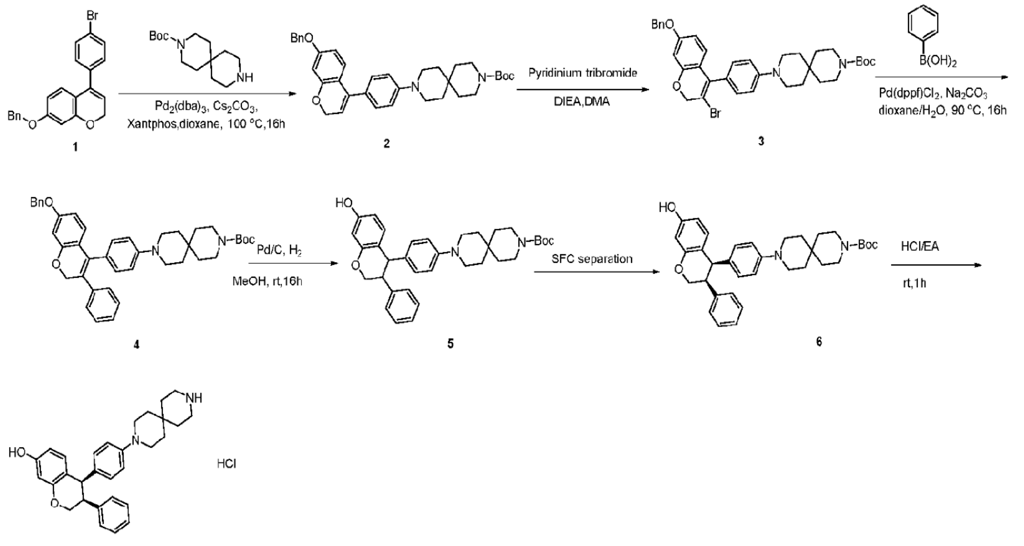
*Step 3: benzyl 7-(dimethoxymethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate*

**[0370]** A solution of benzyl (E)-7-(methoxymethylene)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (4.5 g, 16 mmol, 1 eq.) in Formic acid (20 mL) was stirred at room temperature for 4 hours. 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 hours. 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*

**[0371]** 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 hours under $H_2$ (1 atm). The catalyst was removed by filtration and the filtrate was concentrated to afford 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.5 g, crude, ca. 100% yield) as a white solid.

**Intermediate 21: (3S,4R)-4-(4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)-3-phenylchroman-7-ol hydrochloride**




I-21

*Step 1: tert-butyl 9-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate*

**[0372]** To a mixture of 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene (3.7 g, 9.4 mmol, 1 eq.), tert-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate(2.4 g, 9.4 mmol, 1 eq.), $Pd_2(dba)_3$(861 mg, 0.94 mmol, 0.1 eq.), Xantphos(545 mg, 0.94 mmol, 0.1 eq.), $CS_2CO_3$(6.14 g, 18.8 mmol, 2 eq.) in dioxane (20 mL). The mixture was purged with $N_2$ and heated to 100 °C for 16 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 0-30% EtOAc/hexane to give tert-butyl 9-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate as a yellow solid. (0.77 g, 14 % yield), LC-MS purity: 100% (UV at 254 nm), 567.4 $[M+H]^+$.

*Step 2: tert-butyl 9-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate*

**[0373]** To a solution of tert-butyl 9-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (0.77 g, 1.36 mmol, 1.00 eq) and DIEA (0.35 g, 2.7 mmol, 2.00 eq) in DMA (300 mL), was added pyridinium tribromide (521 mg, 1.63 mmol, 1.2 eq) at 0° C., and the mixture was stirred at 25° C for 1 h. TLC (PE:EA=3:1) showed the starting material was consumed completely. The mixture was poured into $H_2O$ (30 mL), extracted with EtOAc (20 mLx2), and the organic layer was washed with brine (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 tert-butyl 9-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (535 mg, 61%) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 645.4 $[M+H]^+$.

*Steps 3: tert-butyl 9-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate*

**[0374]** To a mixture of tert-butyl 9-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (535 mg, 0.83 mmol, 1.00 eq) in dioxane (10 mL) and $H_2O$ (2 mL), was added phenylboronic acid (121 mg, 1 mmol, 1.2 eq), $Na_2CO_3$ (176 g, 1.66 mmol, 2.00 eq) and Pd(dppf)$Cl_2$ (61 mg, 0.08 mmol, 0.1 eq), and the mixture was stirred at 90 °C for 12 hours. TLC (PE:EA=5:l) showed the starting material was consumed completely. 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 silica gel column chromatography using 0-30% EtOAc/hexane to afford tert-butyl 9-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (430 mg, 81% yield) as yellow solid. LC-MS purity: 100% (UV at 254 nm), 643.5 $[M+H]^+$.

*Steps 4: tert-butyl 9-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate*

**[0375]** To a solution of tert-butyl 9-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (430 mg, 0.67 mmol, 1.00 eq) in MeOH (10 mL) was added Pd/C (100 mg, 10% on carbon, wetted with c.a.55% water) stirred at rt overnight under $H_2$. The mixture was filtered, and the filtrate was concentrated in vacuum to afford tert-butyl 9-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate(380 mg, crude) as white solid. LC-MS purity: 100% (UV at 254 nm), 555.1 $[M+H]^+$.

*Steps 5: Two single isomers of tert-butyl 9-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-*diazaspiro[5.5]undecane-3-carboxylatert-butyl 9-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (380 mg) was purified via SFC as method below to afford two single isomers (P1:150 mg, P2: 150 mg), LC-MS purity: 100% (UV at 254 nm), 555.1 $[M+H]^+$.

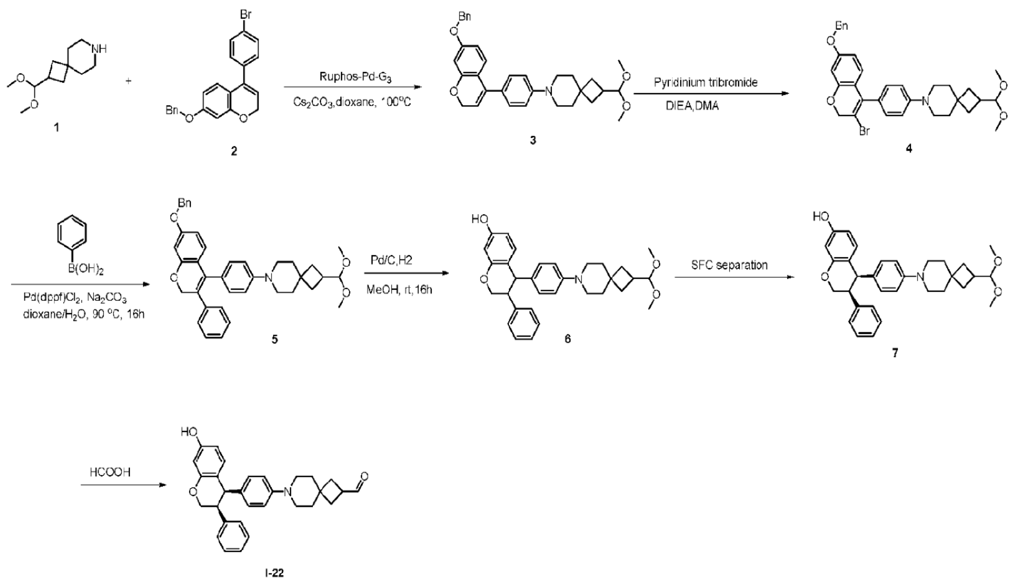
| | |
|---|---|
| **System：** | Waters SFC 150 |
| **Column name:** | DAICELCHIRALPAK®AS |
| **Column size：** | 250*25 mm 10 μm |

| | |
|---|---|
| **Mobile Phase A:** | Supercritical $CO_2$, |
| **Mobile Phase B:** | MEOH (+0.1% 7.0mol/l Ammonia in MEOH) |
| **A:B:** | 75:25 |
| **Wavelength:** | 214 nm |
| **Flow:** | 70ml/min |
| **Column temp:** | RT |
| **Back Pressure:** | 100 bar |
| **Injection:** | 1mL |
| **Cycle time:** | 3.8min |
| **Solvent:** | MeOH: redistilled grade<br>Supercritical $CO_2$: Food grade |

*Steps 6: (3S,4R)-4-(4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)-3-phenylchroman-7-ol hydrochloride*

**[0376]** To a mixture of tert-butyl 9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (160 mg, 0.29 mmol, 1 eq.) in HCl/EA (3 mL). The mixture was stirred at rt for 1 h. The after reaction was direct concentration as to give (3S,4R)-4-(4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)-3-phenylchroman-7-ol hydrochloride as a white soild (140 mg, yield 100%). LC/MS (ESI) m/z: 455.4. Rt: 0.922 min.

**Intermediate 22: 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde**




*Step 1: 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane*

**[0377]** To a mixture of 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene (11 g, 28 mmol, 1 eq), 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (5.6 g, 28 mmol, 1 eq), RuphosPdG$_3$(1.17 g, 1.4 mmol, 0.05 eq), $Cs_2CO_3$(18.2 g, 56 mmol, 2 eq.) in dioxane (50 mL). The mixture was purged with $N_2$ and heated to 100 °C for 16 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 0-30% EtOAc/hexane to give 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane as yellow solid. (9 g, 63% yield), LC-MS purity: 100% (UV at 254 nm),512.4 $[M+H]^+$.

*Step 2: 7-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane*

**[0378]** To a solution of 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.6 g, 3.13 mmol, 1.00 eq) and DIEA (0.8 mg, 6.3 mmol, 2.00 eq) in DMA (10 mL), was added pyridinium tribromide (1.5 mg, 4.7 mmol, 1.5 eq) at 0°C, and the mixture was stirred at 25° C for 1 hour. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture was poured into $H_2O$ (30 mL), extracted with EtOAc (20 mLx2), and the organic layer was washed with brine (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)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1 g, 54% yield) as a yellow solid. LC-MS purity: 100% (UV at 254 nm),590.0 $[M+H]^+$.

*Steps 3: 7-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane*

**[0379]** To a mixture of 7-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.4 g, 2.4 mmol, 1.00 eq) in dioxane (10 mL) and $H_2O$ (2 mL), was added phenylboronic acid (318 mg, 2.6 mmol, 1.1 eq), $Na_2CO_3$ (360 g, 3.4 mmol, 2.00 eq) and Pd(dppf)$Cl_2$ (223 mg, 0.24 mmol, 0.1 eq), and the mixture was stirred at 90°C for 12 h. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture was poured into $H_2O$ (50 mL), extracted with EtOAc (20 mL). The organic layer was washed with brine (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-(7-

(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (0.9 mg, 64% yield) as yellow solid. LC-MS purity: 100% (UV at 254 nm),588.4 [M+H]$^+$.

*Steps 4: 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-3-phenylchroman-7-o*

**[0380]** To a solution of 7-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (0.9 mg, 1.5 mmol, 1.00 eq) in MeOH (10 mL) was added Pd/C (100 mg, 10% on carbon, wetted with c.a.55% water) stirred at room temperature overnight under $H_2$. The mixture was filtered, and the filtrate was concentrated in vacuum to afford 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-3-phenylchroman-7-ol (500 mg, 67% yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), 500.5 [M+H]$^+$.

*Step 5: Two single isomers of 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-3-*

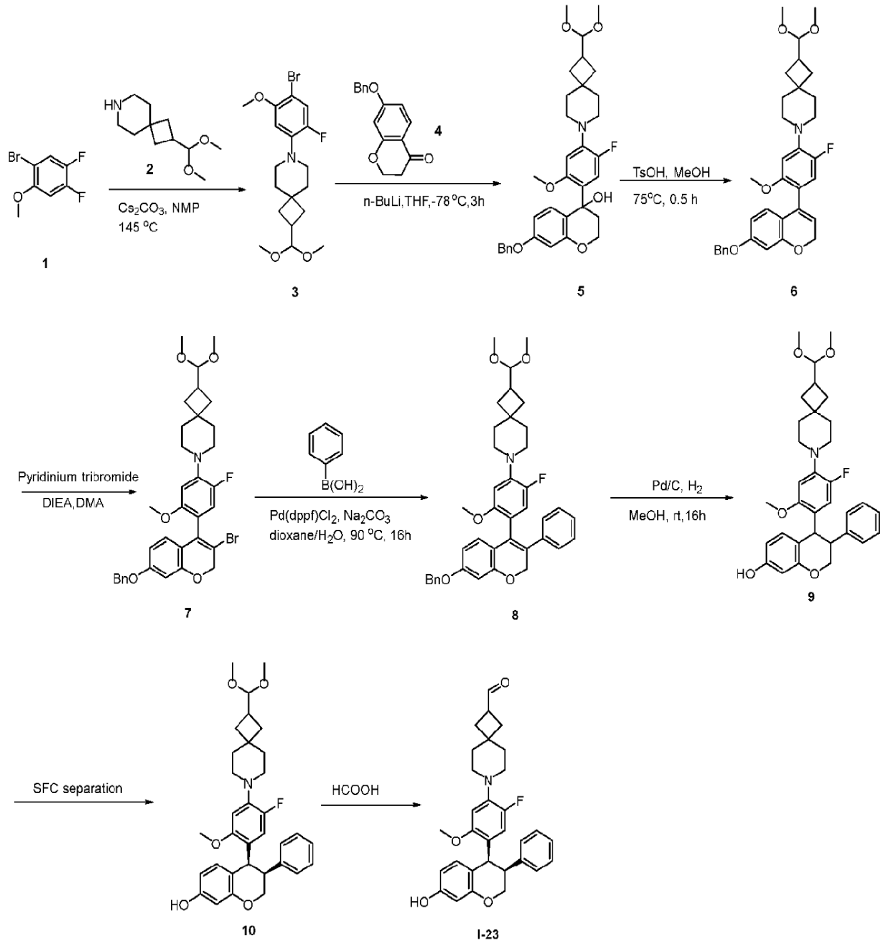
phenylchroman-7-ol-4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-3-phenylchroman-7-ol (500 mg) was purified via SFC as method below to afford two single isomers (isomer 1:240 mg, isomer 2: 220 mg), LC-MS purity: 100% (UV at 254 nm), 500.5 [M+H]$^+$.

| | |
|---|---|
| **Sample Name：** | |
| **System：** | Waters SFC 150 |
| **Column name:** | DAICELCHIRALPAK®AD |
| **Column size：** | 250*25mm 10 µm |
| **Mobile Phase A：** | Supercritical $CO_2$, |
| **Mobile Phase B：** | MeOH (+0.1% 7.0mol/l Ammonia in MeOH) |
| **A:B:** | 45:55 |
| **Wavelength：** | 214 nm |
| **Flow:** | 80ml/min |
| **Column temp:** | RT |
| **Back Pressure:** | 100 bar |
| **Injection:** | 4mL |
| **Cycle time:** | 5.5min |
| **Solvent:** | MeOH: redistilled grade<br>Supercritical $CO_2$: Food grade |
| **Preparation of sample solution:** | sample was dissolved in about 50 mL MeOH:DCM(1:1) |

*Step 6: 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyd*

**[0381]** To a mixture of 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-3-phenylchroman-7-ol (300 mg, 0.6 mmol, 1.00 eq) in FA (3 mL), and the mixture was stirred at rt for 1 hour. The mixture was concentrated in vacuum to afford 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (300 mg, crude) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 454.4 $[M+H]^+$.

**Intermediate 23: 7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde**




*Step 1: 7-(4-bromo-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane*

**[0382]** To a mixture of 1-bromo-4,5-difluoro-2-methoxybenzene (10 g, 44.8 mmol, 1 eq.) and 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane(4.46 g, 22.4 mmol, 0.5 eq.) in NMP (50 mL) was added $Cs_2CO_3$ (29.2 g, 89.7 mmol, 2 eq.), the mixture was stirred at 145°C overnight under $N_2$. The mixture was poured into $H_2O$ (200 mL), extracted with EtOAc (50 mLx2), and the combined organic layer was washed with brine (50.0 mL), dried over $Na_2SO4$, filtered and concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-20%

EtOAc/hexane to afford 7-(4-bromo-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (2.5 g, 28% yield) as a yellow oil. LC-MS purity: 100% (UV at 254 nm), 402.1 $[M+H]^+$.

*Step 2: 7-(benzyloxy)-4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)chroman-4-ol*

**[0383]** To a mixture of 7-(4-bromo-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (2.5 g, 6.2 mmol, 1 eq.) in dry THF (10 mL) was added n-BuLi (1.6 M, 5 mL, 1.30 eq.), the mixture was stirred at -78°C for 1 h, then 7-(benzyloxy)chroman-4-one (1.4 g, 5.6 mmol, 0.9 eq.) was added and the mixture was stirred at -78°C for 1 h. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture was poured into $H_2O$ (30 mL), extracted with EtOAc (20 mL), and 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 silica gel column chromatography using 0-30% EtOAc/hexane to afford 7-(benzyloxy)-4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)chroman-4-ol (460 mg, 14% yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), 578.5 $[M+H]^+$

*Step 3: 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane*

**[0384]** To a solution of 7-(benzyloxy)-4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)chroman-4-ol (460 mg, 0.8 mmol, 1.00 eq) in MeOH (8 mL), was added TsOH (3 mg, 0.02 mmol, 0.02 eq), and the mixture was stirred at 75°C for 30 min. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-20% EtOAc/hexane to afford 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (390 mg, 87% yield) as a yellow solid.

*Step 4: 7-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane*

**[0385]** To a solution of 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (390 mg, 0.7 mmol, 1 eq.) and DIEA (180 mg, 1.39 mmol, 2 eq.) in DMA (10 mL), was added pyridinium tribromide (267 mg, 0.84 mmol, 1.2 eq.) at 0° C, and the mixture was stirred at room temperature for 1 hour. The mixture was poured into $H_2O$ (30 mL), extracted with EtOAc (20 mL), and the organic layer was washed with brine (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 (380 mg, 85% yield) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 638.3 $[M+H]^+$.

*Steps 5: 7-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane*

**[0386]** 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 (380 mg, 0.6 mmol, 1.00 eq) in dioxane (10 mL) and $H_2O$ (2 mL), was added phenylboronic acid (87 mg, 0.71 mmol, 1.2 eq), $Na_2CO_3$ (126 g, 1.19 mmol, 2.00 eq) and Pd(dppf)$Cl_2$ (44 mg, 0.06 mmol, 0.1 eq), and the mixture was stirred at 90°C for 12 h. TLC (PE:EA=5:1) showed the starting material was consumed completely. 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 silica gel column chromatography using 0-30% EtOAc/hexane to afford 7-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (320 mg,84% yield) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 636.5 $[M+H]^+$.

*Steps 6: 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-3-phenylchroman-7-ol*

**[0387]** To a solution of 7-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (320 mg, 0.5 mmol, 1eq) in MeOH (10 mL) was added Pd/C (100 mg, 10% on carbon, wetted with c.a.55% water) stirred at rt overnight under $H_2$. The mixture was filtered, and the filtrate was concentrated in vacuum to afford 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-3-phenylchroman-7-ol (180 mg, 66 % yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), 548.4$[M+H]^+$.

*Step 7: Two single isomers of 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-3-phenylchroman-7-ol*

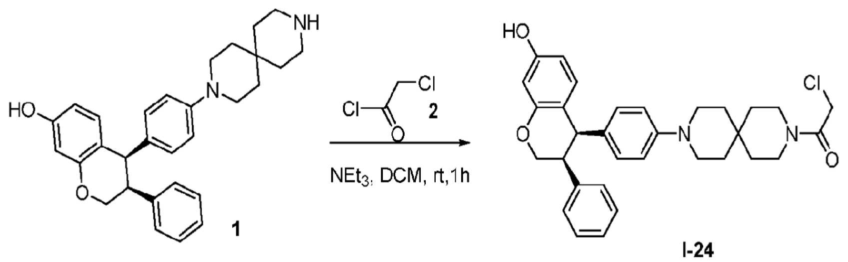
**[0388]** 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-3-phenylchroman-7-ol (180 mg) was purified via SFC as method below to afford two single isomers (P1:80 mg, P2: 80 mg), LC-MS purity: 100% (UV at 254 nm), 548.4$[M+H]^+$.

| | |
|---|---|
| **Sample Name：** | |
| **System：** | Waters SFC 150 |
| **Column name:** | DAICELCHIRALPAK®IC |
| **Column size：** | 250*25 mm 10 µm |
| **Mobile Phase A：** | Supercritical $CO_2$, |
| **Mobile Phase B：** | MeOH (+0.1% 7.0mol/l Ammonia in MeOH) |
| **A:B:** | 45:55 |
| **Wavelength：** | 214 nm |
| **Flow:** | 70ml/min |
| **Column temp:** | RT |
| **Back Pressure:** | 100 bar |
| **Injection:** | 2mL |
| **Cycle time:** | 4.5min |
| **Solvent:** | MeOH : redistilled grade<br>Supercritical $CO_2$ : Food grade |
| **Preparation of sample solution:** | sample was dissolved in about 40Ml MeOH：DCM（1：1） |

*Steps 8: 7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde*

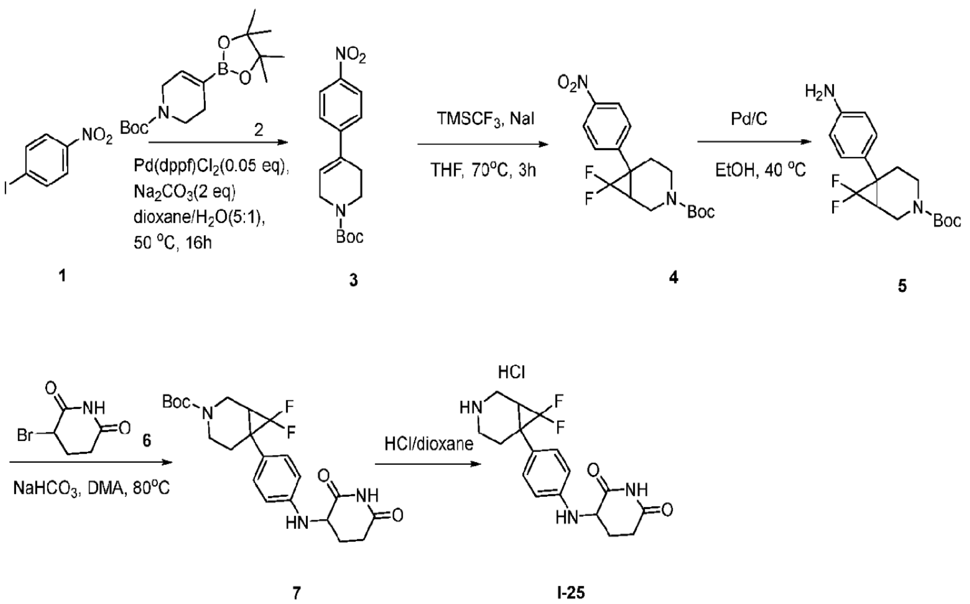
**[0389]** To a mixture of (3S,4S)-4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-3-phenylchroman-7-ol (87 mg, 0.16 mmol, 1.00 eq) in FA (2 mL), and the mixture was stirred at rt for 1 h. The mixture was concentrated in vacuum to afford 7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (85 mg,crude) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 502.4 $[M+H]^+$

**Intermediate 24: 2-chloro-1-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethan-1-one**



**[0390]** To a mixture of (3S,4R)-4-(4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)-3-phenylchroman-7-ol hydrochloride (140 mg, 0.3 mmol, 1.00 eq) in DCM (6 mL) was added TEA (62 mg, 0.62 mmol, 2 eq) and 2-chloroacetyl chloride (36.5 mg, 0.32 mmol, 1.05 eq), and the mixture was stirred at rt for 1 h. The mixture was poured into $H_2O$ (20 mL), extracted with DCM (10 mLx2). The combined organic layer was washed with brine (20 mL), 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 2-chloro-1-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethan-1-one (160 mg, crude) as a yellow oil. LC-MS purity: 100% (UV at 254 nm), 531.4 $[M+H]^+$

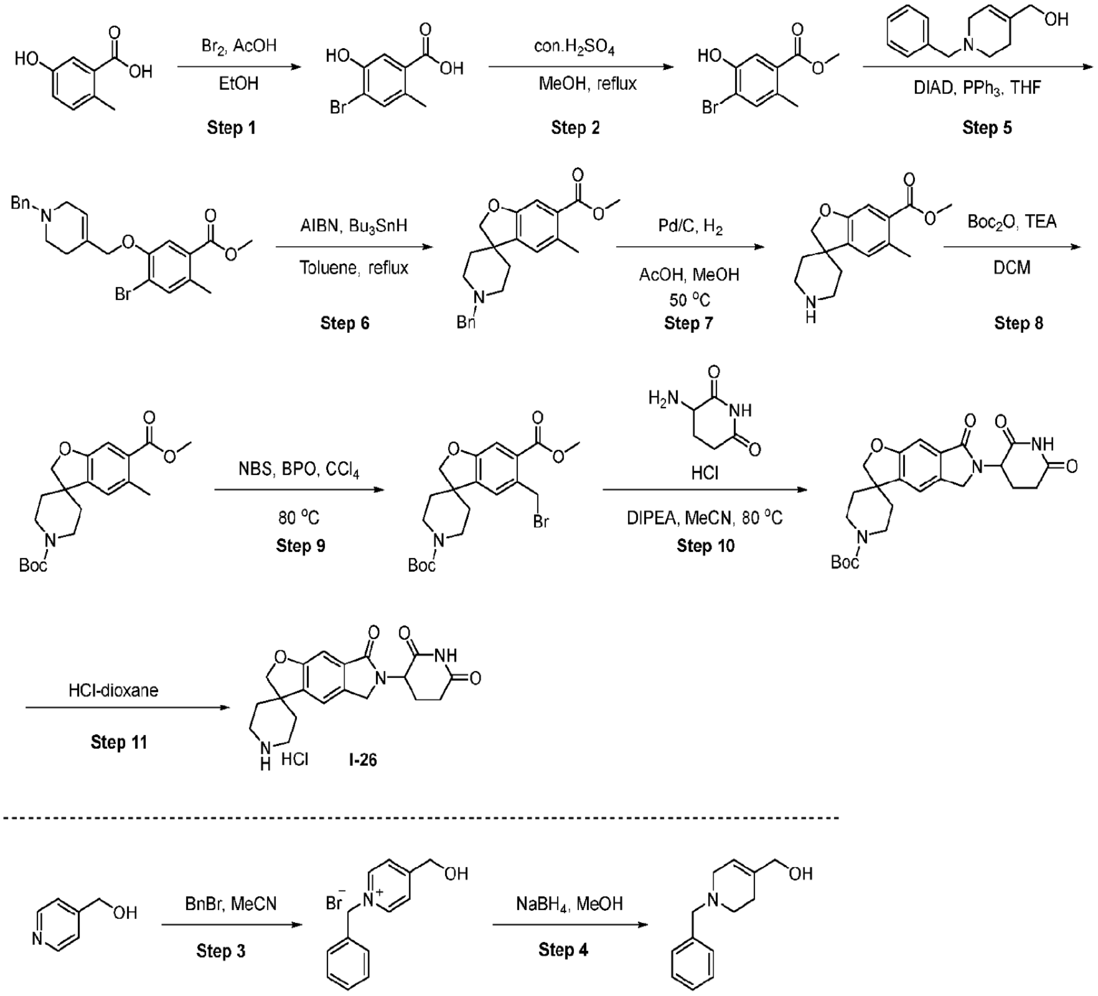
**Intermediate 25. 3-((4-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt**




*Step 1: tert-butyl 4-(4-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate*

**[0391]** 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.

**Intermediate 26. 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.*

**[0392]** 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*

**[0393]** 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 $[M+H]^+$.

**[0394]** $^1$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*

**[0395]** 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 ℃ 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*

**[0396]** 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 ℃. The mixture was stirred at -20 ℃ 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 $[M+H]^+$.

**[0397]** $^1$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*

**[0398]** 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*

**[0399]** 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 $[M+H]^+$.

**[0400]** $^1$H 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*

**[0401]** 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*

**[0402]** 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*

**[0403]** 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*

**[0404]** 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, $(M+H)^+$.

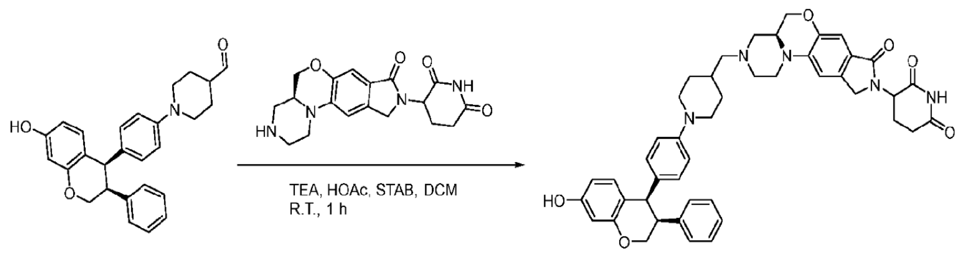
*Step 11: 3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione*

**[0405]** 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 $[M+H]^+$.

**[0406]** $^1$H 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).

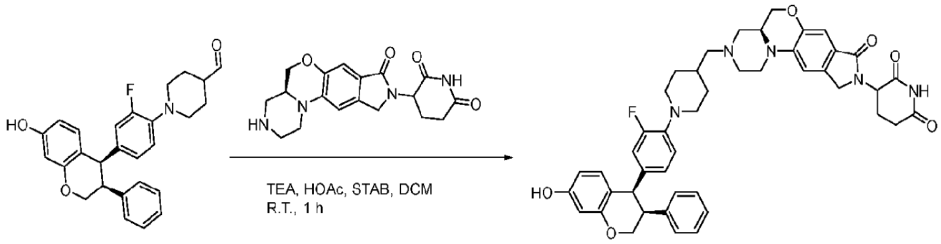
**Compound A1 : 3-((S)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione**




**[0407]** To a mixture of 1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidine-4-carbaldehyde (30 mg, 0.073 mmol, 1 eq.), 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 (34 mg, 0.087 mmol, 1.2 eq.), TEA (11 mg, 0.109 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (7.4 mg, 0.12 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (31 mg, 0.15 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 3-((S)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 (27 mg, 49.1% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 794.2 $[M+H]^+$

**[0408]** 1H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.26 (s, 1H), 7.18 – 7.09 (m, 3H), 6.99 (d, J = 44.2 Hz, 2H), 6.81 – 6.72 (m, 2H), 6.64 (dd, J = 19.4, 8.4 Hz, 3H), 6.42 – 6.24 (m, 4H), 5.06 – 4.98 (m, 1H), 4.38 – 4.10 (m, 6H), 3.85 (d, J = 37.8 Hz, 2H), 3.60 – 3.47 (m, 3H), 3.17 (s, 1H), 3.01 – 2.82 (m, 3H), 2.41 – 2.03 (m, 7H), 1.81 – 1.62 (m, 4H), 1.24 (s, 4H).

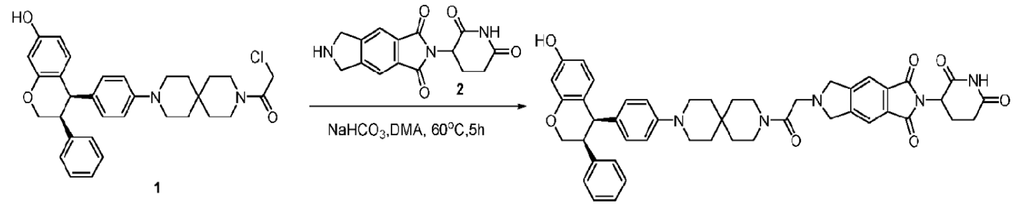
**Compound A2 : 3-((S)-3-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione**




**[0409]** To a mixture of 1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidine-4-carbaldehyde (100 mg, 0.23 mmol, 1 eq.), 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 (109 mg, 0.28 mmol, 1.2 eq.), TEA (35 mg, 0.35 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (24 mg, 0.39 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (98 mg, 0.46mmol, 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 3-((S)-3-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 (39 mg, 22% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 772.0 $[M+H]^+$

**[0410]** $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.33 (s, 1H), 7.17 (t, J = 3.0 Hz,, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.82 – 6.64 (m, 4H), 6.35 – 6.25 (m, 3H), 6.20 – 6.08 (m, 1H), 5.06 – 4.99 (m, 1H), 4.36 – 4.09 (m, 6H), 3.95 – 3.78 (m, 2H), 3.59 – 3.51 (m, 1H), 3.27 – 3.11 (m, 3H), 2.99 – 2.71 (m, 4H), 2.65 – 2.52 (m, 3H), 2.41 – 2.28 (m, 1H), 2.27 – 2.14 (m, 2H), 2.13 – 2.03 (m, 1H), 2.01 – 1.90 (m, 1H), 1.82 – 1.59 (m, 4H), 1.29 – 1.15 (m, 2H).

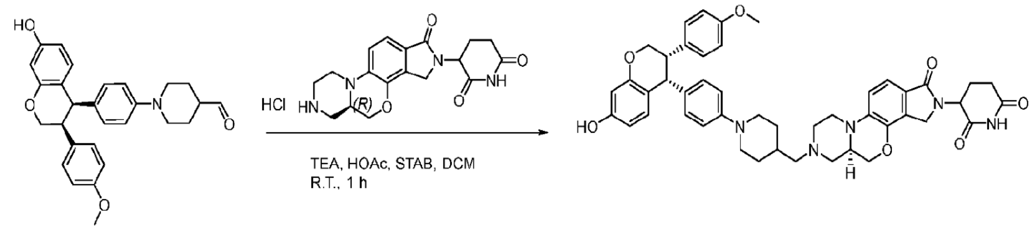
**Compound A3: 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione**




**[0411]** To a mixture of 2-chloro-1-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethan-1-one (160 mg, 0.3 mmol, 1.00 eq) in DMA (5 mL) was added $NaHCO_3$ (76 mg, 0.9 mmol, 3 eq), KI (25 mg，0.35 mmol，0.5 eq) and 2-(2,6-dioxopiperidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione (121 mg, 0.36 mmol, 1.2 eq), and the mixture was stirred at 60°C for 5 h. The mixture was added into HCl（1M） (20 mL), extracted with EA (10 mLx2). The combined organic layer was washed with brine (20 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum. The crude product was purified by pre-HPLC to afford 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione (7.53 mg,3%) as a yellow solid. LC/MS (ESI) m/z: 794.0. Rt：0.747 min.

**[0412]** $^1$H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 8.41 (s, 1H), 7.80 (s, 2H), 7.22 – 7.01 (m, 3H), 6.76 (s, 2H), 6.69 – 6.57 (m, 3H), 6.37 (d, J = 8.4 Hz, 2H), 6.32 – 6.23 (m, 2H), 5.18 – 5.06 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.22 – 4.14 (m, 2H), 4.09 (s, 4H), 3.61 (s, 2H), 3.45 (s, 4H), 3.01 (s, 4H), 2.94 – 2.83 (m, 1H), 2.68 – 2.55 (m, 3H), 2.11 – 2.00 (m, 1H), 1.52 (s, 4H), 1.40 (d, J = 16.4 Hz, 4H).

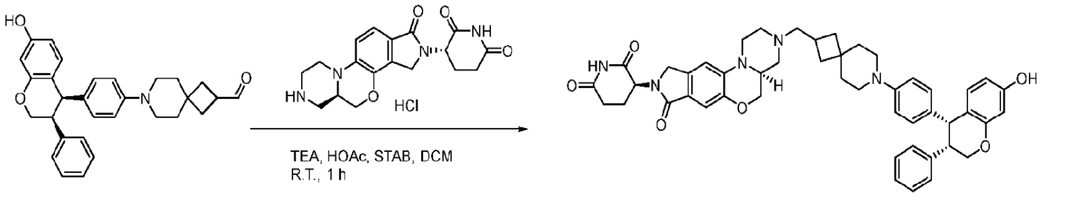
**Compound A16 ： 3-((R)-7-((1-(4-((3S,4R)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione**



**[0413]** To a mixture of 1-(4-((3S,4R)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-yl)phenyl)piperidine-4-carbaldehyde (30 mg, 0.068 mmol, 1 eq.), 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 mg, 0.07 mmol, 1.2 eq.), TEA (10.3 mg, 0.102 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.9 mg, 0.115 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.135 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 3-((R)-7-((1-(4-((3S,4R)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-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 (5.34 mg, 10% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 784.5 $[M+H]^+$

**[0414]** $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.46 (s, 1H), 7.18 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.76 – 6.58 (m, 7H), 6.40 (d, J = 7.8 Hz, 2H), 6.33 – 6.22 (m, 2H), 5.08 – 4.96 (m, 1H), 4.37 – 4.23 (m, 2H), 4.18 – 4.05 (m, 3H), 4.03 – 3.91 (m, 1H), 3.88 – 3.78 (m, 1H), 3.68 (s, 3H), 3.62 – 3.52 (m, 2H), 2.99 – 2.82 (m, 3H), 2.81 – 2.69 (m, 1H), 2.43 – 2.29 (m, 2H), 2.27 – 2.05 (m, 3H), 2.04 – 1.89 (m, 2H), 1.83 – 1.59 (m, 4H), 1.33 – 1.11 (m, 6H).

**Compound A59： (S)-3-((S)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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**

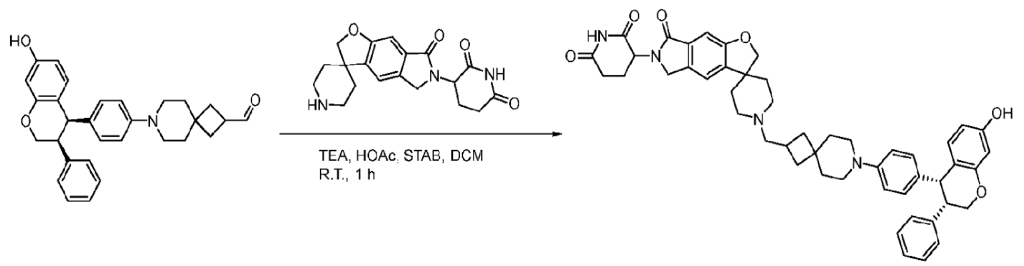


**[0415]** To a mixture of 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), (S)-3-((R)-1-oxo-

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 (31 mg, 0.079 mmol, 1.2 eq.), TEA (10 mg, 0.099 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.7 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 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-((S)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 (23 mg, 44% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 794.5 $[M+H]^+$

**[0416]** $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.28 (s, 1H), 7.18 – 7.09 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.80 – 6.71 (m, 2H), 6.69 – 6.57 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.24 (m, 2H), 5.06 – 4.98 (m, 1H), 4.36 – 4.11 (m, 6H), 3.94 – 3.74 (m, 2H), 3.53 – 3.49 (m, 1H), 3.17 – 3.11 (m, 1H), 3.01 – 2.83 (m, 7H), 2.79 – 2.69 (m, 1H), 2.63 – 2.53 (m, 2H), 2.44 – 2.33 (m, 3H), 2.16 – 2.03 (m, 1H), 2.01 – 1.87 (m, 3H), 1.75 – 1.59 (m, 3H), 1.54 – 1.36 (m, 4H).

**Compound A71 : 3-(1'-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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**

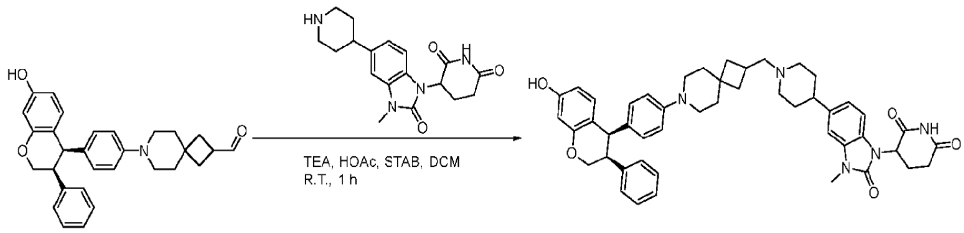



**[0417]** To a mixture of 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), (S)-3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione hydrochloride (31 mg, 0.079 mmol, 1.2 eq.), TEA (10 mg, 0.099 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.7 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 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 3-(1'-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 (9.84 mg, 19% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 793.5 $[M+H]^+$

**[0418]** $^1$H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 8.20 (s, 1H), 7.44 (s, 1H), 7.21 – 7.08 (m, 3H), 7.00 (s, 1H), 6.82 – 6.54 (m, 5H), 6.44 – 6.20 (m, 4H), 5.12 – 5.02 (m, 1H), 4.50 – 4.40 (m, 2H), 4.38 – 4.27 (m, 2H), 4.25 – 4.14 (m, 3H), 3.53 – 3.50 (m, 1H), 3.01 – 2.95 (m, 2H), 2.93 – 2.85 (m, 3H), 2.79 (d, J = 9.4 Hz, 2H), 2.64 – 2.54 (m, 1H), 2.45 – 2.30 (m, 4H), 2.02 – 1.84 (m, 7H), 1.71 – 1.57 (m, 4H), 1.55 – 1.46 (m, 2H), 1.41 (t, J = 9.8 Hz, 2H).

**Compound A73 : 3-(5-(1-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione**

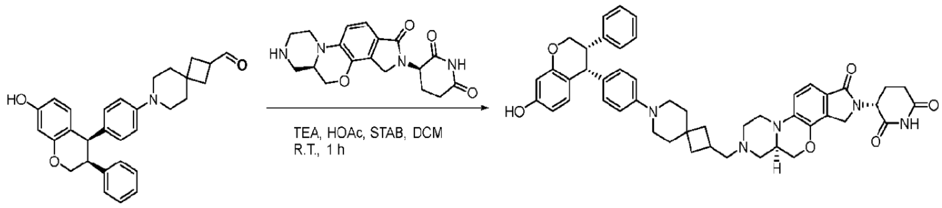



**[0419]** To a mixture of 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), 3-(3-methyl-2-oxo-5-(piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione hydrochloride (30 mg, 0.079 mmol, 1.2 eq.), TEA (10 mg, 0.099 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.7 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 (0-50%Acetonitrile/ 0.05% Formic acid)) to afford 3-(5-(1-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (5.55 mg, 11% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 780.5$[M+H]^+$

**[0420]** $^1$H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 8.30 (s, 1H), 7.17 – 7.07 (m, 4H), 7.01 – 6.87 (m, 2H), 6.79 – 6.73 (m, 2H), 6.67 – 6.58 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.24 (m, 2H), 5.37 – 5.29 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.17 (t, J = 6.8 Hz, 2H), 3.52 – 3.50 (m, 1H), 3.32

(s, 3H), 3.01 – 2.95 (m, 2H), 2.94 – 2.86 (m, 5H), 2.73 – 2.58 (m, 2H), 2.44 – 2.34 (m, 4H), 2.02 – 1.88 (m, 5H), 1.72 – 1.60 (m, 6H), 1.54 – 1.47 (m, 2H), 1.45 – 1.36 (m, 2H).

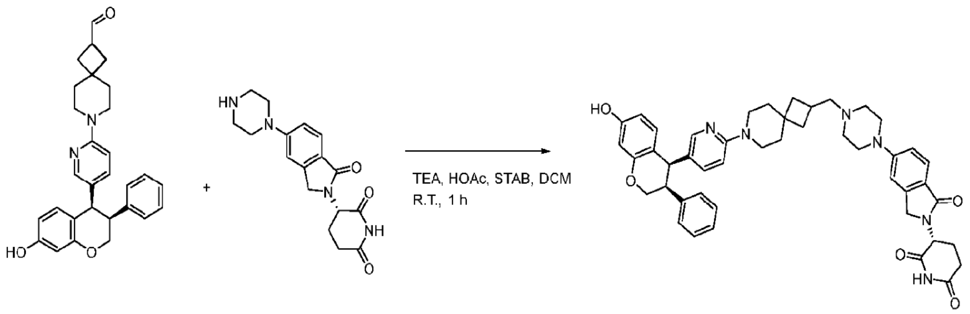
**Compound A89： (R)-3-((R)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione**




**[0421]** To a mixture of 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (120 mg, 0.26 mmol, 1 eq.), (R)-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 (125 mg, 0.32 mmol, 1.2 eq.), TEA (40 mg, 0.396 mmol, 1.5 eq.) in DCM (5.0 mL) was added acetic acid (27 mg, 0.45 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (112 mg, 0.529 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 (R)-3-((R)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 (70 mg, 34% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 794.3 $[M+H]^+$

**[0422]** $^1$H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.23 (s, 1H), 7.24 – 7.08 (m, 4H), 7.00 (d, J = 8.4 Hz, 1H), 6.80 – 6.72 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 8.6 Hz, 2H), 6.37 (d, J = 8.6 Hz, 2H), 6.33 – 6.23 (m, 2H), 5.09 – 4.90 (m, 1H), 4.36 – 4.08 (m, 6H), 4.01 – 3.90 (m, 1H), 3.80 (d, J = 11.4 Hz, 1H), 3.52 – 3.47 (m, 1H), 3.18 – 3.12 (m, 1H), 3.01 – 2.94 (m, 2H), 2.92 – 2.82 (m, 5H), 2.77 – 2.67 (m, 1H), 2.61 – 2.53 (m, 2H), 2.43 – 2.37 (m, 3H), 2.10 (t, J = 10.2 Hz, 1H), 2.00 – 1.88 (m, 3H), 1.73 (t, J = 10.6 Hz, 1H), 1.67 – 1.58 (m, 2H), 1.56 – 1.36 (m, 4H).

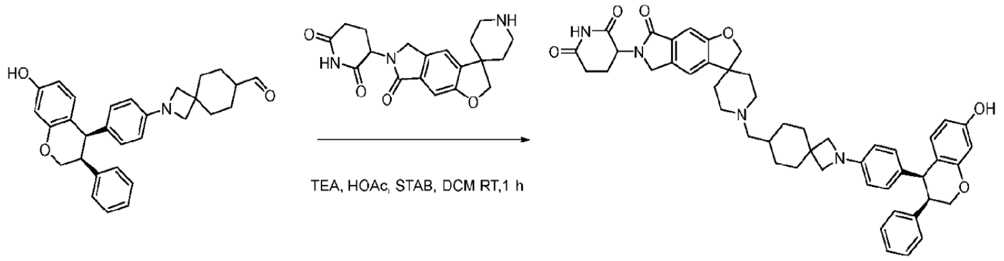
**Compound A92 : (R)-3-(5-(4-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione**




**[0423]** To a mixture of 7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonane-2-carbaldehyde (100 m g, 0.22 mmol 1 eq), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (120 mg, 0.33 mmol 1.5 eq), TEA (33.33 mg, 0.33 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (22.4 mg, 0.37 mmol, 1.7 eq) followed by sodium triacetoxyborohydride (93 mg, 0.44 mmol 2.0 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 (R)-3-(5-(4-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (47.49 mg, 28.2 % yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 767.5 $[M+H]^+$

**[0424]** $^1$H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 8.30 (s, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.28 – 7.13 (m, 4H), 7.04 (d, J = 7.8 Hz, 2H), 6.90 – 6.78 (m, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.52 (d, J = 8.8 Hz, 1H), 6.36 – 6.25 (m, 2H), 5.13 – 4.96 (m, 1H), 4.33 – 4.14 (m, 5H), 3.36 – 3.21 (m, 10H), 2.96 – 2.85 (m, 1H), 2.65 – 2.56 (m, 1H), 2.50 – 2.34 (m, 8H), 2.02 – 1.87 (m, 3H), 1.59 – 1.48 (m, 2H), 1.46 – 1.36 (m, 4H).

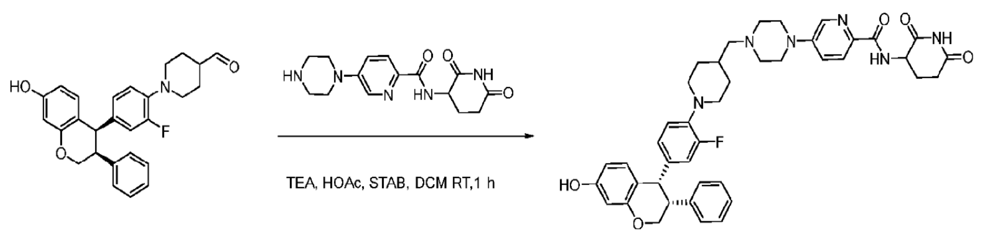
**Compound A99 : 3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione**




**[0425]** To a mixture of 2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), 3-(7-oxo-5,7-dihydro-2H,6H-1'l2-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (23 mg, 0.072 mmol, 1.2 eq.), TEA (6.7 mg, 0.066 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.9 mg, 0.132 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 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 rac-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 (8.5 mg, 16.3% yield) as white solid. LC-MS purity: 99.7% (UV at 254 nm), 793.4 $[M+H]^+$

**[0426]** $^1$H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 7.45 (s, 1H), 7.24 – 7.07 (m, 3H), 7.00 (s, 1H), 6.82 – 6.72 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.39 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.07 (dd, J = 13.2, 5.2 Hz, 1H), 4.49 – 4.40 (m, 2H), 4.37 – 4.27 (m, 2H), 4.25 – 4.11 (m, 3H), 3.54 – 3.46 (m, 2H), 3.42 – 3.39 (m, 2H), 3.37 – 3.33 (m, 2H), 2.95 – 2.78 (m, 3H), 2.62 – 2.55 (m, 1H), 2.41 – 2.30 (m, 1H), 2.12 (d, J = 6.8 Hz, 2H), 2.02 – 1.79 (m, 7H), 1.73 – 1.60 (m, 4H), 1.55 – 1.37 (m, 3H), 0.98 – 0.83 (m, 2H).

**Compound A100 : N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide**

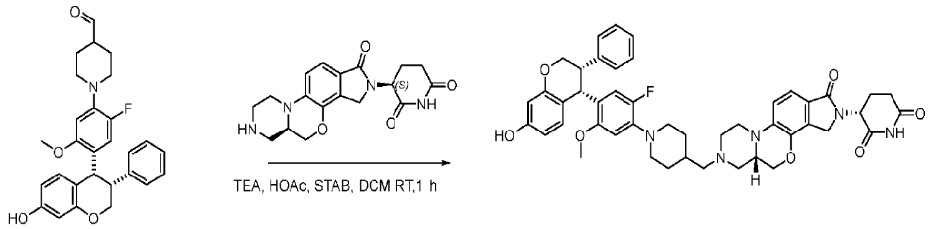



**[0427]** To a mixture of 1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidine-4-carbaldehyde (30 mg, 0.070 mmol, 1 eq.), N-(2,6-dioxopiperidin-3-yl)-5-

(piperazin-1-yl)picolinamide (22 mg, 0.084 mmol, 1.2 eq.), TEA (7.1 mg, 0.070 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (8.4 mg, 0.140 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (30 mg, 0.140 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 rac-N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide (12.82 mg, 25.1% yield) as white solid. LC-MS purity: 99.1% (UV at 254 nm), 793.4 $[M+H]^+$.

**[0428]** $^1$H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.38 – 8.22 (m, 1H), 7.92 – 7.76 (m, 1H), 7.47 – 7.28 (m, 1H), 7.21 – 7.10 (m, 3H), 6.85 – 6.58 (m, 4H), 6.35 – 6.23 (m, 3H), 6.15 (d, J = 13.2 Hz, 1H), 4.81 – 4.69 (m, 1H), 4.40 – 4.08 (m, 3H), 3.61 – 3.48 (m, 2H), 3.41 – 3.14 (m, 9H), 2.97 – 2.64 (m, 2H), 2.60 – 2.53 (m, 2H), 2.38 – 1.90 (m, 5H), 1.81 – 1.59 (m, 3H), 1.34 – 1.08 (m, 2H).

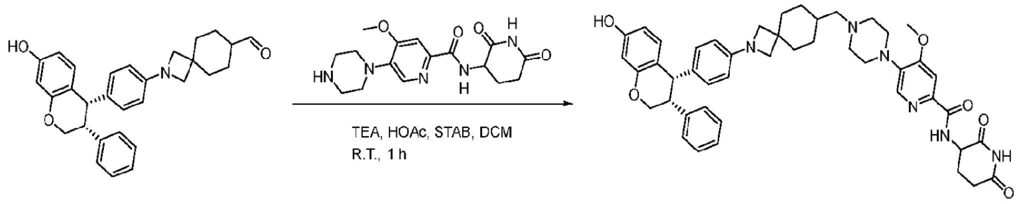
**Compound A106：(R)-3-((S)-7-((1-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione**




**[0429]** To a mixture of 1-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidine-4-carbaldehyde (30 mg, 0.065 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 (28 mg, 0.078 mmol, 1.2 eq.), TEA (6.5 mg, 0.065 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.8 mg, 0.130 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.130 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 (R)-3-((S)-7-((1-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-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 (28.18 mg, 54.1% yield) as a yellow solid. LC-MS purity: 98.4% (UV at 254 nm),802.4 [M+H]$^+$.

**[0430]** $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.32 (s, 1H), 7.22 – 6.96 (m, 5H), 6.77 – 6.55 (m, 3H), 6.36 – 6.20 (m, 4H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.66 (d, J = 5.6 Hz, 1H), 4.38 – 4.20 (m, 3H), 4.14 – 4.04 (m, 2H), 4.03 – 3.91 (m, 1H), 3.83 (d, J = 11.2 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.29 – 3.22 (m, 2H), 3.21 – 3.14 (m, 1H), 3.06 (s, 3H), 2.97 – 2.85 (m, 3H), 2.80 – 2.68 (m, 1H), 2.66 – 2.52 (m, 3H), 2.43 – 2.32 (m, 1H), 2.27 – 2.18 (m, 2H), 2.14 – 2.04 (m, 1H), 2.01 – 1.90 (m, 1H), 1.85 – 1.59 (m, 4H), 1.36 – 1.17 (m, 2H).

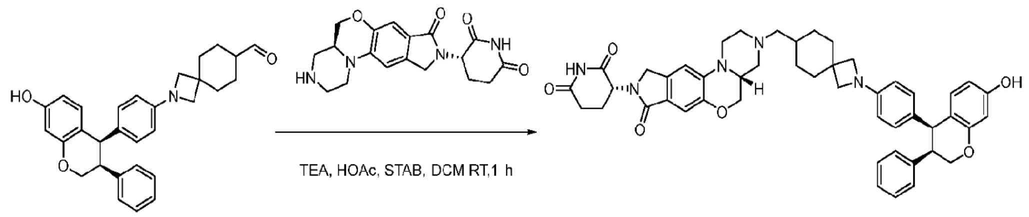
**Compound A117 : N-(2,6-dioxopiperidin-3-yl)-5-(4-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide**




**[0431]** To a mixture of 2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), N-(2,6-dioxopiperidin-3-yl)-4-methoxy-5-(piperazin-1-yl)picolinamide (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 N-(2,6-dioxopiperidin-3-yl)-5-(4-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.5% (UV at 254 nm), 785.1 [M+H]$^+$.

**[0432]** $^1$H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 9.26 (s, 1H), 8.86 (d, J = 8.2 Hz, 1H), 8.05 (s, 1H), 7.57 (s, 1H), 7.14 (s, 3H), 6.76 (s, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.40 – 6.22 (m, 4H), 6.09 (d, J = 8.3 Hz, 2H), 4.75 (t, J = 12.9 Hz, 1H), 4.36 – 4.21 (m, 1H), 4.20 – 4.08 (m, 2H), 3.93 (s, 3H), 3.49 (d, J = 11.2 Hz, 2H), 3.13 (s, 6H), 2.89 – 2.55 (m, 2H), 2.38 – 2.09 (m, 4H), 2.11 – 1.97 (m, 2H), 1.90 – 1.60 (m, 4H), 1.41 (s, 1H), 1.00 – 0.84 (m, 2H).

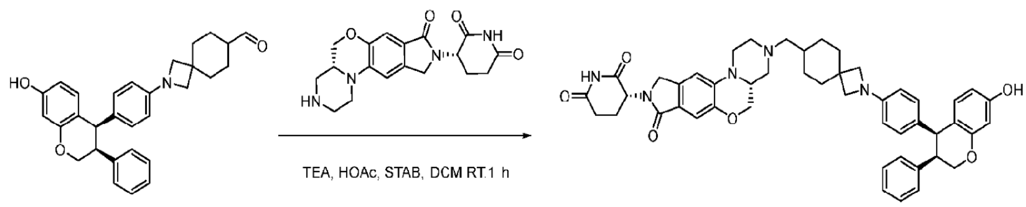
**Compound A118 : (R)-3-((R)-3-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione**




**[0433]** To a mixture of 2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.066 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 (26 mg, 0.072 mmol, 1.1 eq.), TEA (6.7 mg, 0.066 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.9 mg, 0.132 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 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 (R)-3-((R)-3-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 (20.78 mg, 39.5% yield) as a yellow solid. LC-MS purity: 98.4% (UV at 254 nm),794.4 $[M+H]^+$.

**[0434]** $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.27 – 7.10 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.82 – 6.71 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.38 – 6.21 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.37 – 4.09 (m, 6H), 3.92 – 3.77 (m, 2H), 3.51 – 3.47 (m, 1H), 3.41 – 3.32 (m, 5H), 3.18 – 3.12 (m, 1H), 2.96 – 2.84 (m, 3H), 2.80 – 2.71 (m, 1H), 2.62 – 2.54 (m, 1H), 2.39 – 2.30 (m, 1H), 2.17 – 2.03 (m, 3H), 1.98 – 1.91 (m, 1H), 1.87 – 1.76 (m, 2H), 1.75 – 1.62 (m, 3H), 1.54 – 1.38 (m, 3H), 1.00 – 0.80 (m, 2H).

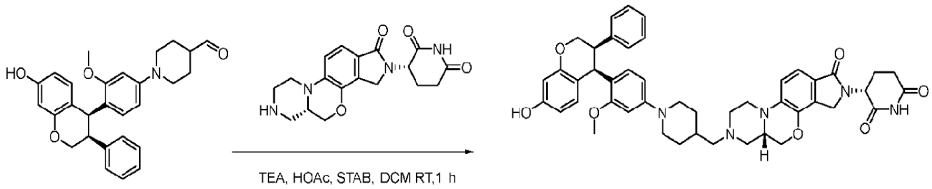
**Compound A120 : (R)-3-((R)-3-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione**



**[0435]** To a mixture of 2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), (S)-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 (26 mg, 0.072 mmol, 1.1 eq.), TEA (6.7 mg, 0.066 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.9 mg, 0.132 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 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 (R)-3-((R)-3-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 (17.59 mg, 34.2% yield) as a white solid. LC-MS purity: 98.4% (UV at 254 nm),794.4 $[M+H]^+$.

**[0436]** $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.19 – 7.05 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.79 – 6.70 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.41 – 6.21 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.38 – 4.23 (m, 3H), 4.21 – 4.07 (m, 3H), 3.93 – 3.78 (m, 2H), 3.51 – 3.47 (m, 1H), 3.43 – 3.30 (m, 5H), 3.18 – 3.12 (m, 1H), 2.94 – 2.83 (m, 3H), 2.78 – 2.71 (m, 1H), 2.61 – 2.54 (m, 1H), 2.38 – 2.28 (m, 1H), 2.18 – 2.02 (m, 3H), 1.98 – 1.90 (m, 1H), 1.88 – 1.77 (m, 2H), 1.75 – 1.62 (m, 3H), 1.55 – 1.33 (m, 3H), 0.98 – 0.80 (m, 2H).

**Compound A121 : (R)-3-((S)-7-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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**



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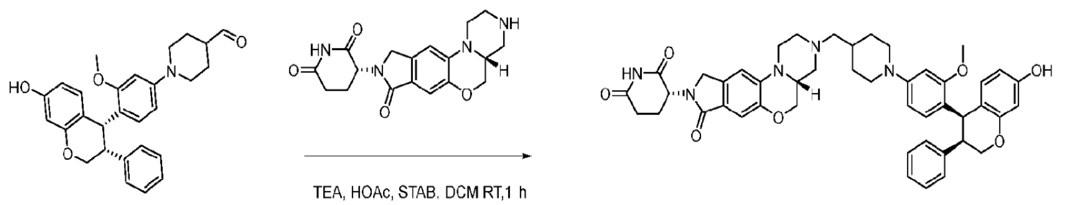
**[0437]** To a mixture of 1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (80 mg, 0.180 mmol, 1 eq.), (S)-3-((S)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (71 mg, 0.198 mmol, 1.1 eq.), TEA (18.2 mg, 0.180 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (21.6 mg, 0.360 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (76 mg, 0.360 mmol, 2.0 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 (R)-3-((S)-7-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 ( 64.14 mg, 45.4% yield) as a white solid.. LC-MS purity: 98.1% (UV at 254 nm), 784.2 $[M+H]^+$.

**[0438]** $^1$H NMR (400 MHz, DMSO) δ 11.18 (s, 1H), 10.94 (s, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.19 – 7.05 (m, 4H), 6.77 – 6.55 (m, 4H), 6.37 – 6.23 (m, 2H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.76 – 4.65 (m, 1H), 4.46 – 4.39 (m, 1H), 4.33 – 4.06 (m, 6H), 3.97 – 3.87 (m, 1H), 3.69 – 3.48 (m, 9H), 3.19 – 3.03 (m, 6H), 2.98 – 2.83 (m, 2H), 2.71 – 2.52 (m, 3H), 2.46 – 2.33 (m, 1H), 2.27 – 1.88 (m, 4H), 1.71 (s, 1H).

**Compound A122 : (R)-3-((R)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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**

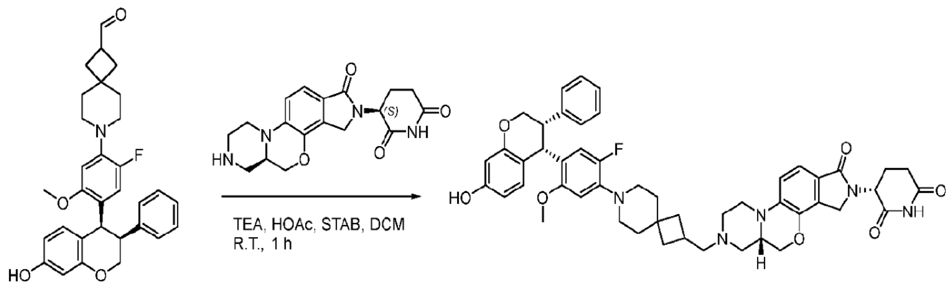



**[0439]** To a mixture of 1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (80 mg, 0.180 mmol, 1 eq.), (R)-3-((R)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (71 mg, 0.198 mmol, 1.1 eq.), TEA (18.2 mg, 0.180 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (21.6 mg, 0.360 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (76 mg, 0.360 mmol, 2.0 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 (R)-3-((R)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 ( 70.36 mg, 49.5% yield) as a white solid.. LC-MS purity: 99.5% (UV at 254 nm), 784.4 $[M+H]^+$.

**[0440]** $^1$H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.29 – 6.95 (m, 5H), 6.71 – 6.41 (m, 5H), 6.38 – 6.18 (m, 3H), 5.08 – 4.99 (m, 1H), 4.65 (d, J = 5.2 Hz, 1H), 4.38 – 4.16 (m, 7H), 4.08 – 4.00 (m, 2H), 3.75 – 3.56 (m, 5H), 3.50 – 3.44 (m, 1H), 3.26 – 3.16 (m, 1H), 3.17 – 3.05 (m, 3H), 2.95 – 2.84 (m, 2H), 2.78 – 2.66 (m, 2H), 2.64 – 2.52 (m, 3H), 2.41 – 2.32 (m, 1H), 2.07 – 1.75 (m, 4H), 1.43 – 1.27 (m, 2H).

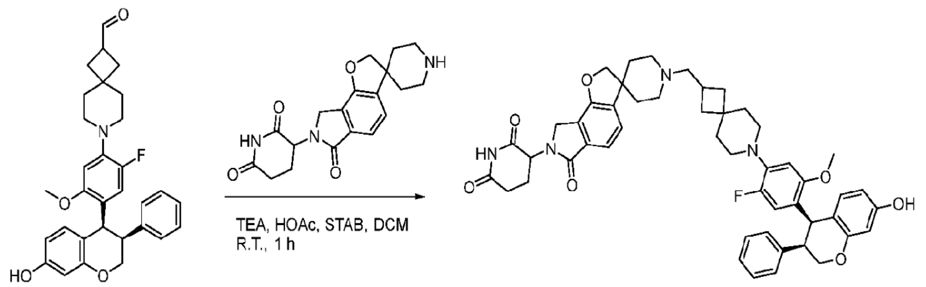
**Compound A125：(R)-3-((S)-7-((7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione**




**[0441]** To a mixture of 7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (35 mg, 0.07 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 (33 mg, 0.084 mmol, 1.2 eq.), TEA (10.6 mg, 0.10 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (7.1 mg, 0.119 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (30 mg, 0.14 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 (R)-3-((S)-7-((7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-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 (10.79 mg, 18% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 842.5 $[M+H]^+$.

[0442] $^1$H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.32 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.14 – 7.07 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.77 – 6.66 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.34 – 6.19 (m, 4H), 5.06 – 4.99 (m, 1H), 4.65 (d, J = 5.2 Hz, 1H), 4.39 – 4.21 (m, 3H), 4.16 – 4.05 (m, 2H), 3.95 (t, J = 9.6 Hz, 1H), 3.80 (d, J = 11.6 Hz, 1H), 3.50 – 3.46 (m, 1H), 3.20 – 3.10 (m, 1H), 3.05 (s, 3H), 2.96 – 2.70 (m, 8H), 2.62 – 2.53 (m, 1H), 2.47 – 2.32 (m, 4H), 2.11 (t, J = 10.2 Hz, 1H), 2.01 – 1.89 (m, 3H), 1.79 – 1.63 (m, 3H), 1.62 – 1.52 (m, 2H), 1.44 (t, J = 9.4 Hz, 2H).

**Compound A130 : 3-(1'-((7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-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**

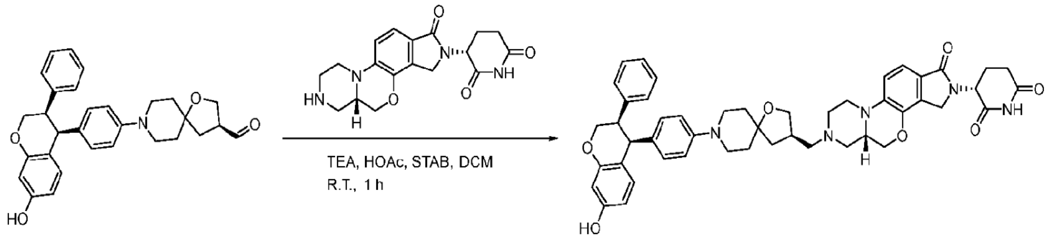



[0443] To a mixture of 7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (35 mg, 0.07 mmol, 1 eq.), 3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione hydrochloride (33 mg, 0.084 mmol, 1.2 eq.), TEA (10.6 mg, 0.10 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (7.1 mg, 0.119 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (30 mg, 0.14 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 3-(1'-((7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-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 (13.71 mg, 23.3% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 841.5 $[M+H]^+$.

[0444] $^1$H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.29 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 3.6 Hz, 3H), 6.78 – 6.68 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.35 – 6.21 (m, 4H), 5.12 – 5.04 (m, 1H), 4.65 (d, J = 5.2 Hz, 1H), 4.55 – 4.46 (m, 2H), 4.42 – 4.27 (m, 2H), 4.21 (d, J = 17.0 Hz, 1H), 4.08 (d, J = 7.8 Hz, 1H), 3.50 – 3.48 (m, 1H), 3.05 (s, 3H), 2.94 –

2.75 (m, 7H), 2.59 (d, J = 16.6 Hz, 1H), 2.47 – 2.33 (m, 4H), 2.05 – 1.84 (m, 7H), 1.72 – 1.52 (m, 6H), 1.43 (t, J = 9.4 Hz, 2H).

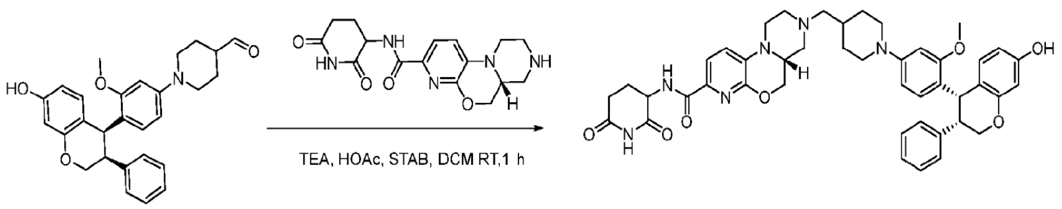
**Compound A132 : (R)-3-((S)-7-(((R)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione**




**[0445]** To a mixture of (S)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), (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-c]isoindol-2-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 (R)-3-((S)-7-(((R)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.8% (UV at 254 nm), 785.1 $[M+H]^+$.

**[0446]** $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.28 (s, 1H), 7.23 – 7.07 (m, 4H), 7.01 (d, J = 8.0 Hz, 1H), 6.80 – 6.70 (m, 2H), 6.69 – 6.55 (m, 3H), 6.37 (d, J = 8.8 Hz, 2H), 6.31 – 6.22 (m, 2H), 5.10 – 4.98 (m, 1H), 4.39 – 4.24 (m, 3H), 4.21 – 4.12 (m, 2H), 4.08 (s, 1H), 4.00 – 3.94 (m, 1H), 3.87 (d, J = 7.8 Hz, 1H), 3.81 (s, 1H), 3.55 – 3.47 (m, 1H), 3.43 (d, J = 7.6 Hz, 1H), 3.33 (s, 4H), 3.06 (s, 3H), 2.88 (d, J = 12.6 Hz, 1H), 2.70 (d, J = 16.0 Hz, 1H), 2.37 – 2.32 (m, 2H), 2.12 (s, 1H), 2.01 – 1.91 (m, 3H), 1.83 – 1.72 (m, 1H), 1.64 – 1.52 (m, 4H), 1.40 – 1.20 (m, 4H).

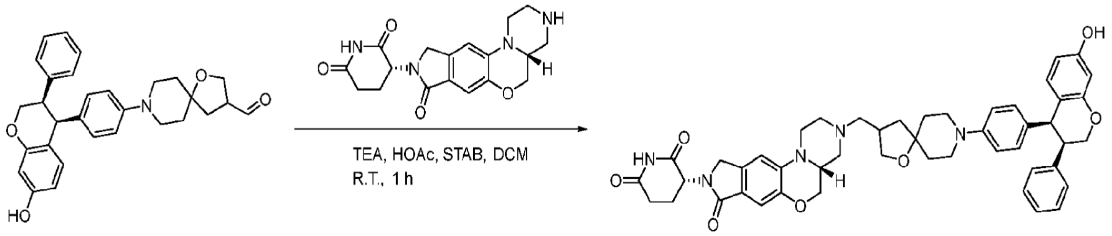
**Compound A134 : (4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide**




**[0447]** To a mixture of 1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (30 mg, 0.068 mmol, 1 eq.), (4aR)-N-(2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide (26 mg, 0.074 mmol, 1.1 eq.), TEA (6.8 mg, 0.068 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (8.1 mg, 0.136 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (29 mg, 0.136 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 (4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide (20.95 mg, 39.9% yield) as a yellow solid. LC-MS purity: 99.6% (UV at 254 nm), 773.4 $[M+H]^+$.

**[0448]** $^1H$ NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.31 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.17 – 7.04 (m, 3H), 6.74 – 6.64 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 7.6 Hz, 1H), 6.31 – 6.21 (m, 2H), 6.18 (s, 1H), 4.76 – 4.66 (m, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.51 – 4.38 (m, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.13 – 4.00 (m, 2H), 3.78 (d, J = 11.6 Hz, 1H), 3.65 – 3.56 (m, 2H), 3.49 – 3.39 (m, 2H), 3.23 – 3.17 (m, 1H), 3.05 – 2.92 (m, 5H), 2.84 – 2.70 (m, 2H), 2.63 – 2.55 (m, 2H), 2.25 – 1.94 (m, 5H), 1.84 – 1.62 (m, 4H), 1.25 – 1.11 (m, 2H).

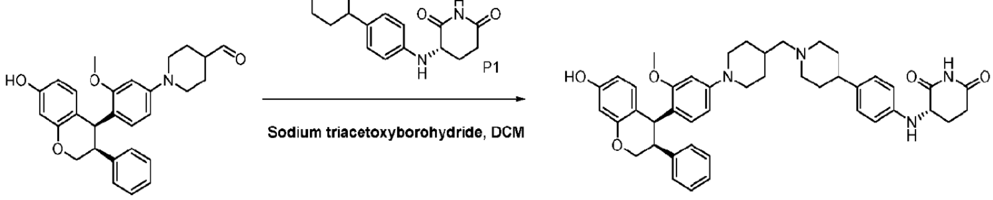
**Compound A139 : (3R)-3-((4aR)-3-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione**




**[0449]** To a mixture of 8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), (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 (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 (3R)-3-((4aR)-3-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.5% (UV at 254 nm), 810.2 $[M+H]^+$.

**[0450]** $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.17 – 7.11 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.80 – 6.72 (m, 2H), 6.69 – 6.57 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.21 (m, 2H), 5.05 – 4.98 (m, 1H), 4.71 – 3.89 (m, 7H), 3.88 – 3.67 (m, 2H), 3.51 (d, J = 4.0 Hz, 1H), 3.44 (t, J = 7.8 Hz, 1H), 3.35 (s, 1H), 3.15 (s, 1H), 3.06 (s, 2H), 2.95 – 2.84 (m, 2H), 2.76 (s, 1H), 2.63 – 2.54 (m, 2H), 2.33 (t, J = 8.8 Hz, 3H), 2.17 – 2.07 (m, 1H), 1.98 – 1.88 (m, 2H), 1.76 – 1.68 (m, 1H), 1.66 – 1.33 (m, 5H), 1.24 (s, 2H).

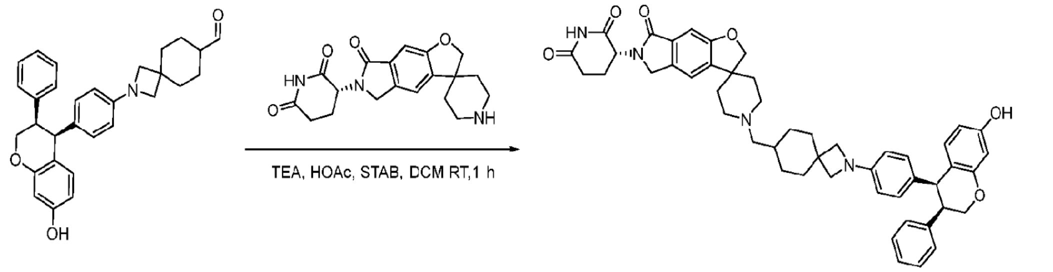
**Compound A149: (S)-3-((4-(1-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione**




**[0451]** To a mixture of 1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (30 m g, 0.068 mmol 1 eq.), (S)-3-((4-(piperidin-4-

yl)phenyl)amino)piperidine-2,6-dione (22 mg, 0.074 mmol 1.1 eq .) in DCM (3 mL) was added sodium triacetoxyborohydride (29 mg, 0.136 mmol 2.0 eq.) at room temperature for 1 hour .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/ 0.01% formic acid) to afford (S)-3-((4-(1-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione (34.35 mg, 70.9 % yield) as a white solid. LC-MS (ESI, m/z): mass calcd. For C44H50N4O5, 714.4; found, 715.2 $[M+H]^+$. $^1$H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 7.10 (s, 3H), 6.95 (d, J = 6.8 Hz, 2H), 6.69 – 6.54 (m, 5H), 6.48 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 8.4 Hz, 1H), 6.30 – 6.22 (m, 2H), 6.17 (s, 1H), 5.64 (d, J = 6.4 Hz, 1H), 4.64 – 4.57 (m, 1H), 4.34 – 4.19 (m, 2H), 4.04 (d, J = 9.6 Hz, 1H), 3.65 – 3.54 (m, 3H), 3.47 – 3.39 (m, 2H), 3.02 (s, 3H), 2.93 (d, J = 10.4 Hz, 2H), 2.78 – 2.67 (m, 1H), 2.60 – 2.53 (m, 3H), 2.36 – 2.26 (m, 1H), 2.21 – 2.06 (m, 3H), 2.01 – 1.92 (m, 2H), 1.80 – 1.72 (m, 2H), 1.70 – 1.52 (m, 5H), 1.23 – 1.08 (m, 2H).

**Compound A153 : (R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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**

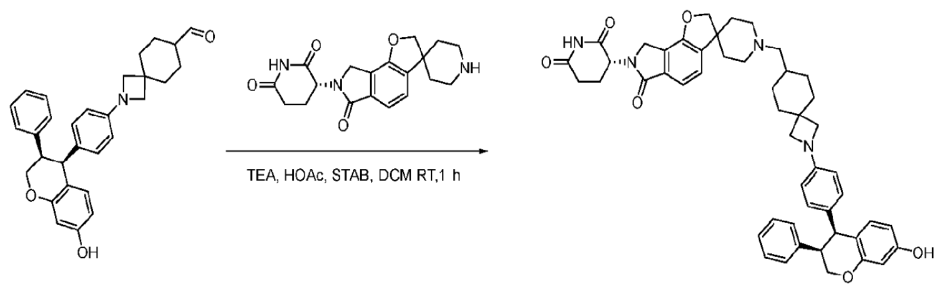



**[0452]** To a mixture of rac-2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), rac-(R)-3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (26 mg, 0.072 mmol, 1.1 eq.), TEA (6.7 mg, 0.068 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.9 mg, 0.132 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 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 (R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 (21.29 mg, 40.6 % yield) as a white solid. LC-MS purity: 99.6% (UV at 254 nm), 793.4 $[M+H]^+$.

**[0453]** $^1$H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 7.45 (s, 1H), 7.22 – 7.08 (m, 3H), 7.00 (s, 1H), 6.81 – 6.71 (m, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.37 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.07 (dd, J = 13.2, 5.2 Hz, 1H), 4.48 – 4.40 (m, 2H), 4.38 – 4.28 (m, 2H), 4.24 – 4.11 (m, 3H), 3.54 – 3.44 (m, 2H), 3.41 – 3.39 (m, 2H), 3.36 – 3.33 (m, 2H), 2.97 – 2.77 (m, 3H), 2.64 – 2.54 (m, 1H), 2.42 – 2.30 (m, 1H), 2.11 (d, J = 6.8 Hz, 2H), 1.99 – 1.80 (m, 7H), 1.73 – 1.63 (m, 4H), 1.53 – 1.38 (m, 3H), 0.98 – 0.83 (m, 2H).

**Compound A154: (R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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**

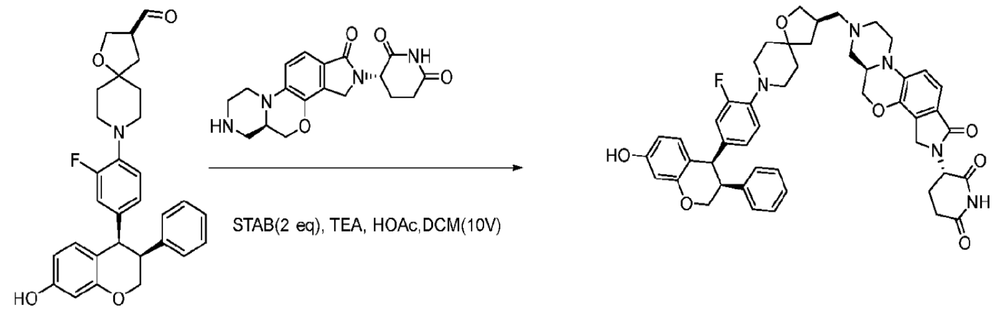



**[0454]** To a mixture of 2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), (R)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (26 mg, 0.072 mmol, 1.1 eq.), TEA (6.7 mg, 0.068 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.9 mg, 0.132 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 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 (R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 (2.11 mg, 4.1% yield) as a gentle red solid. LC-MS purity: 96.8% (UV at 254 nm), 793.4 $[M+H]^+$.

**[0455]** $^1$H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.26 (s, 1H), 7.42 – 7.22 (m, 2H), 7.18 – 7.07 (m, 3H), 6.79 – 6.72 (m, 2H), 6.70 – 6.58 (m, 1H), 6.36 – 6.25 (m, 4H), 6.12 – 6.06 (m, 2H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.51 (s, 2H), 4.40 – 4.29 (m, 2H), 4.24 – 4.13 (m, 3H), 3.52 – 3.46 (m, 1H), 3.44 – 3.37 (m, 2H), 3.38 – 3.34 (m, 2H), 2.99 – 2.73 (m, 3H), 2.63 – 2.56 (m, 1H), 2.46 –

2.27 (m, 1H), 2.18 – 2.06 (m, 2H), 2.02 – 1.79 (m, 6H), 1.74 – 1.64 (m, 3H), 1.53 – 1.37 (m, 3H), 1.28 – 1.21 (m, 2H), 0.98 – 0.83 (m, 2H).

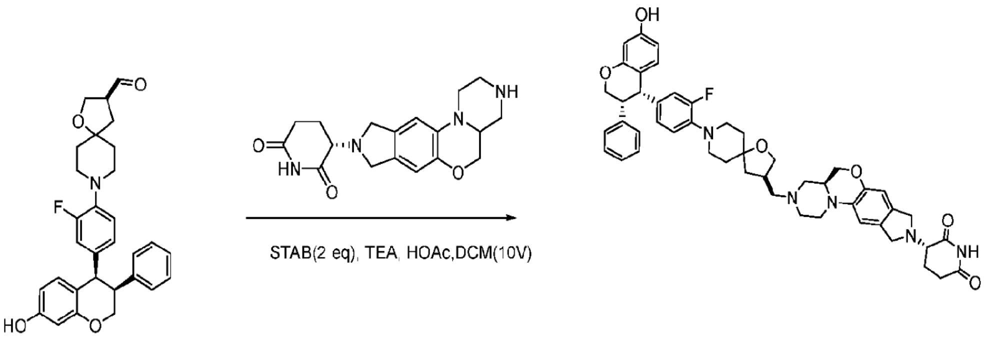
**Compound A157：(S)-3-((R)-7-(((R)-8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione**




**[0456]** To a mixture of (S)-8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (35 mg, 0.072 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 (31mg, 0.09 mmol, 1.2 eq.), TEA (16.1 mg, 0.108 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (7.3 mg, 0.12 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (30.5 mg, 0.14 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-((R)-7-(((R)-8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 (22.53 mg, 38.9% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 828.4 $[M+H]^+$.

**[0457]** $^1$H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.29 (s, 1H), 7.19 – 7.15 (m, 1H), 7.14 – 7.08 (m, 3H), 7.01 (d, J = 8.6 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 – 6.26 (m, 3H), 5.06 – 4.99 (m, 1H), 4.46 (d, J = 5.2 Hz, 1H), 4.38 – 4.22 (m, 3H), 4.17 – 4.06 (m, 2H), 3.99 – 3.78 (m, 3H), 3.56 – 3.48 (m, 2H), 3.16 – 3.08 (m, 5H), 3.04 – 2.98 (m, 1H), 2.94 – 2.84 (m, 2H), 2.76 – 2.66 (m, 2H), 2.39 – 2.32 (m, 3H), 2.17 – 2.04 (m, 1H), 2.00 – 1.90 (m, 2H), 1.82 – 1.70 (m, 1H), 1.68 – 1.53 (m, 4H), 1.38 – 1.30 (m, 1H).

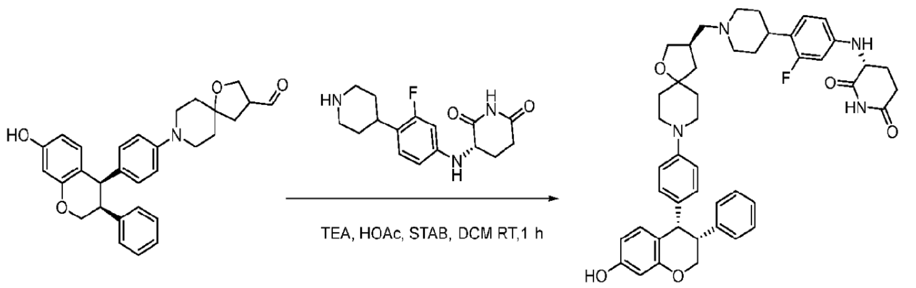
**Compound A161: (S)-3-((S)-3-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione**




**[0458]** To a mixture of (3S,4R)-4-(4-((S)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)-3-fluorophenyl)-3-phenylchroman-7-ol (30 mg, 0.072 mmol, 1 eq.), (3S)-3-(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, 0.09 mmol, 1.2 eq.), TEA (16.1 mg, 0.108 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (7.3 mg, 0.12 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (30.5 mg, 0.14 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-((S)-3-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-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 (7.46 mg, 12.7% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 828.4 $[M+H]^+$.

**[0459]** $^1H$ NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.27 (s, 1H), 7.14 – 7.09 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.78 – 6.74 (m, 2H), 6.66 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 (s, 1H), 6.33 (s, 1H), 6.32 – 6.28 (m, 2H), 6.28 – 6.26 (m, 1H), 5.02 (dd, J = 13.4, 5.0 Hz, 1H), 4.46 (d, J = 5.0 Hz, 1H), 4.38 – 4.25 (m, 3H), 4.22 (s, 1H), 4.18 – 4.10 (m, 2H), 3.93 – 3.85 (m, 2H), 3.84 – 3.77 (m, 1H), 3.18 – 3.08 (m, 6H), 3.06 – 2.83 (m, 4H), 2.76 (s, 2H), 2.37 – 2.32 (m, 3H), 2.13 – 2.04 (m, 1H), 2.01 – 1.89 (m, 3H), 1.72 – 1.57 (m, 5H), 1.38 – 1.31 (m, 1H).

**Compound A162: 3-((3-fluoro-4-(1-(((R)-8-(4-((3RS,4SR)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione**



**[0460]** To a mixture of 8-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (30 mg, 0.064 mmol, 1 eq.), (S)-3-((3-fluoro-4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione (22 mg, 0.070 mmol, 1.1 eq.), TEA (6.4 mg, 0.064 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.6 mg, 0.128 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.128 mmol, 2.0 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 (RS)-3-((3-fluoro-4-(1-(((R)-8-(4-((3RS,4SR)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione (14.85 mg, 30.5% yield) as a white solid. LC-MS purity: 98.7% (UV at 254 nm), 759.5 $[M+H]^+$.

**[0461]** $^1$H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.58 (m, 3H), 6.46 – 6.34 (m, 4H), 6.33 – 6.25 (m, 2H), 5.98 (d, *J* = 7.6 Hz, 1H), 4.36 – 4.27 (m, 2H), 4.20 – 4.14 (m, 2H), 3.84 (d, *J* = 7.2 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.42 (d, *J* = 6.0 Hz, 1H), 3.09 – 3.03 (m, 4H), 2.95 – 2.90 (m, 1H), 2.76 – 2.69 (m, 1H), 2.59 – 2.55 (m, 2H), 2.33 (d, *J* = 7.2 Hz, 2H), 2.10 – 1.83 (m, 6H), 1.73 – 1.49 (m, 9H), 1.32 (dd, *J* = 12.4, 8.0 Hz, 1H).

**[0462]** Compounds shown in the following table were prepared in a manner analogous to Compound **A154** by reductive amination.

**Table 4. Characterization Data for Compounds A1 to A165**

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| **A1** | $^1$H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.26 (s, 1H), 7.18 – 7.09 (m, 3H), 6.99 (d, *J* = 44.2 Hz, 2H), 6.81 – 6.72 (m, 2H), 6.64 (dd, *J* = 19.4, 8.4 Hz, 3H), 6.42 – 6.24 (m, 4H), 5.06 – 4.98 (m, 1H), 4.38 – 4.10 (m, 6H), 3.85 (d, *J* = 37.8 Hz, 2H), 3.60 – 3.47 (m, 3H), 3.17 (s, 1H), 3.01 – 2.82 (m, | B | 754.4 | 754.4 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 3H), 2.41 – 2.03 (m, 7H), 1.81 – 1.62 (m, 4H), 1.24 (s, 4H). | | | |
| **A2** | $^{1}$H NMR (400 MHz, MeOD) δ 7.29 (d, J = 8.4 Hz, 1H), 7.18 – 7.11 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.80 – 6.66 (m, 4H), 6.40 – 6.28 (m, 3H), 6.20 (d, J = 14.0 Hz, 1H), 5.11 – 5.04 (m, 1H), 4.58 (s, 3H), 4.44 – 4.17 (m, 6H), 4.08 – 3.98 (m, 1H), 3.84 (d, J = 10.0 Hz, 1H), 3.61 – 3.50 (m, 1H), 3.09 – 2.72 (m, 5H), 2.65 – 2.54 (m, 2H), 2.53 – 2.39 (m, 1H), 2.36 – 2.08 (m, 4H), 1.93 – 1.56 (m, 4H), 1.44 – 1.25 (m, 4H). | F | 772.3 | 772.3 |
| **A3** | $^{1}$H NMR (400 MHz, CD3OD) δ 7.29 (d, J = 8.4 Hz, 1H), 7.16 – 7.07 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.75 – 6.67 (m, 5H), 6.48 (d, J = 8.6 Hz, 2H), 6.39 – 6.28 (m, 2H), 5.11 – 5.01 (m, 1H), 4.47 – 4.26 (m, 4H), 4.24 – 4.11 (m, 2H), 4.08 – 4.00 (m, 1H), 3.89 – 3.80 (m, 1H), 3.70 – 3.33 (m, 4H), 3.17 – 3.07 (m, 1H), 3.02 – 2.97 (m, 1H), 2.94 – 2.82 (m, 2H), 2.78 – 2.69 (m, 1H), 2.68 – 2.54 (m, 2H), 2.53 – 2.41 (m, 1H), 2.39 – 2.24 (m, 3H), 2.17 – 2.07 (m, 1H), 1.96 – 1.61 (m, 4H), 1.42 – 1.25 (m, 2H). | C | 794.3 | 794.5 |
| **A4** | $^{1}$H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 8.41 (s, 1H), 7.80 (s, 2H), 7.22 – 7.01 (m, 3H), 6.76 (s, 2H), 6.69 – 6.57 (m, 3H), 6.37 (d, J = 8.4 Hz, 2H), 6.32 – 6.23 (m, 2H), 5.18 – 5.06 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.22 – 4.14 (m, 2H), 4.09 (s, 4H), 3.61 (s, 2H), 3.45 (s, 4H), 3.01 (s, 4H), 2.94 – 2.83 (m, 1H), 2.68 – 2.55 (m, 3H), 2.11 – 2.00 (m, 1H), 1.52 (s, 4H), 1.40 (d, J = 16.4 Hz, 4H). | E | 772.3 | 772.3 |
| **A5** | $^{1}$H NMR (400 MHz, DMSO-d6) δ 11.37 (s, 1H), 7.85 (s, 2H), 7.46 (s, 2H), 7.22-7.19 (m, 3H), 6.91 (d, J = 7.6 Hz, 2H), 6.69 (d, J = 8.8 Hz, 1H), | C | 754.4 | 754.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 6.32-6.30 (m, 2H), 5.17-5.12 (m, 1H), 4.29 (d, J = 6.8 Hz, 1H), 4.19 (d, J = 5.6 Hz, 1H), 3.61-3.59 (m, 3H), 3.48-3.45 (m, 2H), 3.41-3.39 (m, 2H), 2.94-2.84 (m, 1H), 2.67-2.56 (m, 1H), 2.08-2.05 (m, 1H), 1.85-1.79 (m, 1H), 1.55-1.48 (m, 11H), 0.95-0.91 (m, 6H). | | | |
| **A6** | $^1$H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.88 (s, 2H), 7.46 (s, 2H), 7.25-7.19 (m, 3H), 6.93-6.91 (m, 2H), 6.88 (d, J = 9.2 Hz, 1H), 6.32-6.30 (m, 2H), 5.17-5.12 (m, 1H), 4.29 (d, J = 7.6 Hz, 1H), 4.20 (d, J = 5.2 Hz, 1H), 3.64-3.56 (m, 4H), 3.49 (s, 2H), 3.39 (s, 2H), 2.94-2.86 (m, 1H), 2.68-2.55 (m, 1H), 2.08-2.05 (m, 1H), 1.85-1.76 (m, 1H), 1.65-1.49 (m, 11H), 0.95-0.93 (m, 6H). | C | 772.4 | 772.5 |
| **A7** | $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.39 (s, 1H), 7.21 – 7.13 (m, 4H), 7.01 (d, J = 8.4 Hz, 1H), 6.86 – 6.62 (m, 4H), 6.37 – 6.22 (m, 3H), 6.20 – 6.08 (m, 1H), 5.09 – 4.96 (m, 1H), 4.41 – 4.16 (m, 5H), 4.10 (d, J = 16.8 Hz, 1H), 4.03 – 3.91 (m, 1H), 3.83 (d, J = 10.2 Hz, 1H), 3.56 – 3.53 (m, 1H), 3.25 – 3.14 (m, 4H), 2.99 – 2.82 (m, 3H), 2.75 (t, J = 11.4 Hz, 1H), 2.61 – 2.53 (m, 2H), 2.44 – 2.33 (m, 1H), 2.27 – 2.05 (m, 3H), 1.98 – 1.90 (m, 1H), 1.84 – 1.56 (m, 4H), 1.34 – 1.13 (m, 2H). | E | 754.4 | 754.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| **A8** | $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.20 – 7.11 (m, 4H), 7.01 (d, J = 8.4 Hz, 1H), 6.81 – 6.72 (m, 2H), 6.69 – 6.57 (m, 3H), 6.38 (d, J = 8.6 Hz, 2H), 6.33 – 6.23 (m, 2H), 5.07 – 4.99 (m, 1H), 4.39 – 4.06 (m, 6H), 4.03 – 3.93 (m, 1H), 3.83 (d, J = 11.2 Hz, 1H), 3.59 – 3.47 (m, 3H), 3.30 (s, 1H), 3.22 – 3.13 (m, 1H), 2.98 – 2.83 (m, 3H), 2.80 – 2.70 (m, 1H), 2.63 – 2.53 (m, 2H), 2.42 – 2.35 (m, 1H), 2.24 – 2.05 (m, 3H), 2.00 – 1.91 (m, 1H), 1.80 – 1.59 (m, 4H), 1.24 – 1.10 (m, 2H). | E | 754.3 | 754.6 |
| **A9** | $^1$H NMR (400 MHz, MeOD) δ 7.29 (d, J = 8.4 Hz, 1H), 7.18 – 7.11 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.80 – 6.66 (m, 4H), 6.40 – 6.28 (m, 3H), 6.20 (d, J = 14.0 Hz, 1H), 5.11 – 5.04 (m, 1H), 4.58 (s, 3H), 4.44 – 4.17 (m, 6H), 4.08 – 3.98 (m, 1H), 3.84 (d, J = 10.0 Hz, 1H), 3.61 – 3.50 (m, 1H), 3.09 – 2.72 (m, 5H), 2.65 – 2.54 (m, 2H), 2.53 – 2.39 (m, 1H), 2.36 – 2.08 (m, 4H), 1.93 – 1.56 (m, 4H), 1.44 – 1.25 (m, 4H). | F | 772.3 | 772.3 |
| **A10** | $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H), 7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H). | B | 756.4 | 756.5 |
| **A11** | $^1$H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.26 (s, 1H), 7.18 – 7.09 (m, 3H), 6.99 (d, *J* = 44.2 Hz, 2H), 6.81 – 6.72 (m, 2H), 6.64 (dd, *J* = 19.4, 8.4 Hz, 3H), 6.42 – 6.24 (m, 4H), 5.06 – 4.98 (m, 1H), 4.38 – 4.10 (m, 6H), 3.85 (d, *J* = 37.8 Hz, 2H), 3.60 – 3.47 (m, 3H), 3.17 (s, 1H), 3.01 – 2.82 (m, | B | 754.4 | 754.4 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 3H), 2.41 – 2.03 (m, 7H), 1.81 – 1.62 (m, 4H), 1.24 (s, 4H). | | | |
| **A12** | $^{1}$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.26 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.75 – 6.58 (m, 7H), 6.40 (d, J = 8.6 Hz, 2H), 6.33 – 6.21 (m, 2H), 5.07 – 4.98 (m, 1H), 4.39 – 4.21 (m, 3H), 4.17 – 4.06 (m, 3H), 4.03 – 3.92 (m, 1H), 3.83 (d, J = 9.8 Hz, 1H), 3.68 (s, 3H), 3.62 – 3.40 (m, 3H), 3.23 – 3.12 (m, 1H), 3.00 – 2.84 (m, 3H), 2.75 (t, J = 11.2 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.43 – 2.35 (m, 1H), 2.25 – 2.14 (m, 2H), 1.99 – 1.91 (m, 1H), 1.81 – 1.62 (m, 4H), 1.29 – 1.10 (m, 5H). | F | 784.4 | 784.5 |
| **A13** | $^{1}$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.75 – 6.59 (m, 7H), 6.40 (d, J = 8.4 Hz, 2H), 6.34 – 6.22 (m, 2H), 5.07 – 4.98 (m, 1H), 4.39 – 4.22 (m, 3H), 4.17 – 4.07 (m, 3H), 4.02 – 3.93 (m, 1H), 3.83 (d, J = 10.8 Hz, 1H), 3.68 (s, 3H), 3.56 (d, J = 10.2 Hz, 2H), 3.48 – 3.42 (m, 1H), 3.23 – 3.13 (m, 1H), 3.00 – 2.83 (m, 3H), 2.75 (t, J = 10.8 Hz, 1H), 2.62 – 2.52 (m, 3H), 2.44 – 2.32 (m, 1H), 2.25 – 2.06 (m, 3H), 2.01 – 1.90 (m, 1H), 1.84 – 1.61 (m, 5H), 1.25 – 1.09 (m, 2H). | F | 784.4 | 784.5 |
| **A14** | $^{1}$H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 9.32 (s, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.25 – 7.13 (m, 4H), 7.03 (s, 1H), 6.82 – 6.64 (m, 4H), 6.36 – 6.24 (m, 3H), 6.15 (d, J = 14.8 Hz, 1H), 5.69 – 5.59 (m, 1H), 4.36 – 4.17 (m, 3H), 3.59 – 3.50 (m, 1H), 3.22 (d, J = 10.0 Hz, 2H), 3.10 (s, 4H), 2.90 – 2.78 (m, 1H), 2.74 – 2.64 (m, 2H), 2.61 – 2.52 (m, 5H), 2.41 (s, 3H), 2.27 – 2.15 (m, 3H), 1.82 – 1.57 (m, 3H), 1.30 – 1.16 (m, 3H). | F | 743.4 | 743.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| **A15** | $^1$H NMR (400 MHz, MeOD) δ 7.67 (s, 1H), 6.50 (d, J = 8.4 Hz, 1H), 6.22 (d, J = 8.4 Hz, 1H), 5.97 – 5.79 (m, 7H), 5.71 (d, J = 8.4 Hz, 2H), 5.57 – 5.47 (m, 2H), 4.33 – 4.23 (m, 1H), 3.63 – 3.45 (m, 4H), 3.38 – 3.19 (m, 3H), 3.06 (d, J = 11.6 Hz, 1H), 2.93 (s, 3H), 2.84 – 2.62 (m, 3H), 2.33 – 1.93 (m, 5H), 1.83 (t, J = 11.8 Hz, 2H), 1.73 – 1.30 (m, 5H), 1.16 – 0.88 (m, 4H), 0.61 – 0.45 (m, 2H). | E | 784.4 | 784.5 |
| **A16** | $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.46 (s, 1H), 7.18 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.76 – 6.58 (m, 7H), 6.40 (d, J = 7.8 Hz, 2H), 6.33 – 6.22 (m, 2H), 5.08 – 4.96 (m, 1H), 4.37 – 4.23 (m, 2H), 4.18 – 4.05 (m, 3H), 4.03 – 3.91 (m, 1H), 3.88 – 3.78 (m, 1H), 3.68 (s, 3H), 3.62 – 3.52 (m, 2H), 2.99 – 2.82 (m, 3H), 2.81 – 2.69 (m, 1H), 2.43 – 2.29 (m, 2H), 2.27 – 2.05 (m, 3H), 2.04 – 1.89 (m, 2H), 1.83 – 1.59 (m, 4H), 1.33 – 1.11 (m, 6H). | E | 784.4 | 784.5 |
| **A17** | $^1$H NMR (400 MHz, MeOD) δ 7.44 (d, J = 9.2 Hz, 1H), 7.32 – 7.22 (m, 1H), 7.21 – 7.05 (m, 4H), 6.75 – 6.64 (m, 5H), 6.48 (d, J = 8.6 Hz, 2H), 6.39 – 6.27 (m, 2H), 5.61 – 5.52 (m, 1H), 4.57 (s, 2H), 4.41 (t, J = 11.0 Hz, 1H), 4.22 – 4.13 (m, 2H), 3.56 – 3.45 (m, 1H), 3.26 (s, 2H), 3.06 – 3.00 (m, 2H), 2.98 – 2.91 (m, 6H), 2.89 – 2.82 (m, 3H), 2.79 – 2.73 (m, 1H), 2.69 – 2.63 (m, 1H), 2.50 (s, 3H), 2.39 – 2.28 (m, 1H), 2.15 – 2.04 (m, 2H), 1.85 – 1.71 (m, 2H), 1.67 – 1.52 (m, 4H), 1.37 – 1.24 (m, 3H). | F | 765.4 | 765.6 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| **A18** | $^{1}$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H), 7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H). | B | 756.4 | 756.5 |
| **A19** | $^{1}$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H), 7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H). | B | 756.4 | 756.5 |
| **A20** | $^{1}$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H), 7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H). | B | 756.4 | 756.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| **A21** | $^{1}$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.26 (s, 1H), 7.20 – 7.09 (m, 4H), 7.00 (d, J = 8.4 Hz, 1H), 6.80 – 6.71 (m, 2H), 6.68 – 6.56 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.23 (m, 2H), 5.11 – 4.92 (m, 1H), 4.36 – 4.04 (m, 6H), 4.02 – 3.90 (m, 1H), 3.80 (d, J = 10.6 Hz, 1H), 3.54 – 3.48 (m, 1H), 3.17 – 3.11 (m, 1H), 3.02 – 2.81 (m, 7H), 2.76 – 2.66 (m, 1H), 2.63 – 2.53 (m, 2H), 2.43 – 2.30 (m, 3H), 2.17 – 1.87 (m, 4H), 1.79 – 1.58 (m, 3H), 1.55 – 1.34 (m, 4H). | F | 794.4 | 794.4 |
| **A22** | $^{1}$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.36 (s, 1H), 7.21 – 7.09 (m, 4H), 7.00 (d, J = 8.0 Hz, 1H), 6.75 (s, 2H), 6.68 – 6.56 (m, 3H), 6.42 – 6.23 (m, 4H), 5.06 – 4.99 (m, 1H), 4.36 – 4.08 (m, 6H), 4.00 – 3.92 (m, 1H), 3.84 – 3.78 (m, 1H), 3.52 – 3.49 (m, 1H), 3.16 – 3.12 (m, 1H), 3.00 – 2.84 (m, 7H), 2.76 – 2.67 (m, 1H), 2.61 – 2.54 (m, 2H), 2.43 – 2.34 (m, 3H), 2.16 – 1.88 (m, 4H), 1.78 – 1.59 (m, 3H), 1.53 – 1.37 (m, 4H). | F | 794.4 | 794.4 |
| **A23** | $^{1}$H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.27 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.09 – 6.97 (m, 2H), 6.77 – 6.60 (m, 4H), 6.49 – 6.21 (m, 6H), 5.03 (dd, *J* = 13.2, 4.8 Hz, 1H), 4.41 – 4.05 (m, 6H), 4.02 – 3.78 (m, 2H), 3.61 – 3.43 (m, 6H), 3.23 – 3.12 (m, 1H), 2.99 – 2.83 (m, 3H), 2.81 – 2.69 (m, 1H), 2.62 – 2.53 (m, 3H), 2.46 – 2.31 (m, 2H), 2.27 – 1.88 (m, 5H), 1.27 – 1.15 (m, 4H). | C | 784.4 | 784.5 |
| **A24** | $^{1}$H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.26 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.09 – 6.99 (m, 2H), 6.73 – 6.61 (m, 4H), 6.46 – 6.23 (m, 6H), 5.03 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.41 – 4.21 (m, 3H), 4.21 – 4.06 (m, 3H), 3.98 (dd, *J* = 19.4, 9.2 Hz, 1H), 3.62 – 3.43 (m, 6H), 3.18 (s, 1H), 3.01 – | C | 784.4 | 784.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 2.82 (m, 3H), 2.60 – 2.55 (m, 2H), 2.46 – 2.28 (m, 2H), 2.27 – 2.05 (m, 3H), 1.97 – 1.90 (m, 1H), 1.85 – 1.61 (m, 4H), 1.29 – 1.10 (m, 4H). | | | |
| **A25** | $^1$H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.32 (s, 1H), 7.40 (d, J = 9.2 Hz, 1H), 7.27 – 7.08 (m, 4H), 7.02 (s, 1H), 6.81 – 6.70 (m, 2H), 6.68 – 6.56 (m, 3H), 6.43 – 6.23 (m, 4H), 5.67 – 5.60 (m, 1H), 4.32 (t, J = 11.2 Hz, 1H), 4.22 – 4.12 (m, 2H), 3.53 – 3.48 (m, 2H), 3.10 – 3.03 (m, 4H), 3.01 – 2.96 (m, 2H), 2.93 – 2.87 (m, 2H), 2.85 – 2.79 (m, 1H), 2.72 – 2.65 (m, 2H), 2.56 – 2.52 (m, 3H), 2.46 – 2.38 (m, 6H), 2.24 – 2.17 (m, 1H), 1.92 (t, J = 9.6 Hz, 2H), 1.68 – 1.59 (m, 2H), 1.56 – 1.48 (m, 2H), 1.47 – 1.38 (m, 2H). | F | 764.4 | 764.4 |
| **A26** | $^1$H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.35 (s, 1H), 7.80 (s, 2H), 7.15-7.13 (m, 3H), 6.76-6.66 (m, 2H), 6.64-6.61 (m, 3H), 6.37 (d, J = 8.4 Hz, 2H), 6.30-6.25 (m, 2H), 5.15-5.12 (m, 1H), 4.33-4.30 (m, 1H), 4.18-4.16 (m, 2H), 4.10 (s, 4H), 3.88 (s, 2H), 3.60 (s, 2H), 3.11-2.94 (m, 4H), 2.62-2.55 (m, 1H), 2.17-2.07 (m, 1H), 1.75-1.73 (m, 4H), 1.74-1.48 (m, 2H), 0.96-0.93 (m, 3H). | F | 766.4 | 766.5 |
| **A27** | $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.36 (s, 1H), 7.18 – 7.09 (m, 3H), 7.03 (s, 1H), 6.92 (s, 1H), 6.79 – 6.71 (m, 2H), 6.69 – 6.56 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.23 (m, 2H), 5.05 – 4.99 (m, 1H), 4.35 – 4.14 (m, 6H), 3.92 – 3.76 (m, 3H), 3.53 – 3.50 (m, 1H), 3.16 – 3.11 (m, 1H), 3.00 – 2.85 (m, 7H), 2.77 – 2.70 (m, 1H), 2.60 – 2.54 (m, 1H), 2.42 – 2.30 (m, 3H), 2.09 (t, J = 10.4 Hz, 1H), 1.98 – 1.88 (m, 3H), 1.77 – 1.59 (m, 3H), 1.54 – 1.37 (m, 4H). | F | 794.4 | 794.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| **A28** | $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.33 (s, 1H), 7.17 – 7.09 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.55 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.24 (m, 2H), 5.07 – 4.97 (m, 1H), 4.35 – 4.12 (m, 6H), 3.92 – 3.76 (m, 3H), 3.52 – 3.50 (m, 1H), 3.17 – 3.11 (m, 1H), 3.00 – 2.84 (m, 7H), 2.77 – 2.68 (m, 1H), 2.61 – 2.53 (m, 1H), 2.43 – 2.32 (m, 3H), 2.14 – 2.04 (m, 1H), 1.98 – 1.88 (m, 3H), 1.75 – 1.59 (m, 3H), 1.53 – 1.37 (m, 4H). | F | 794.4 | 794.5 |
| **A29** | $^1$H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 9.33 (s, 1H), 7.26 – 7.08 (m, 3H), 6.87 – 6.63 (m, 5H), 6.57 – 6.36 (m, 2H), 6.35 – 6.24 (m, 3H), 6.21 – 6.06 (m, 1H), 5.81 (d, J = 7.8 Hz, 1H), 4.37 – 4.17 (m, 4H), 3.59 – 3.51 (m, 1H), 3.21 (d, J = 8.2 Hz, 2H), 2.87 (s, 4H), 2.75 – 2.67 (m, 1H), 2.58 – 2.52 (m, 7H), 2.32 – 2.03 (m, 3H), 1.93 – 1.55 (m, 4H), 1.31 – 1.13 (m, 2H). | F | 722.3 | 722.3 |
| **A30** | $^1$H NMR (400 MHz, DMSO) δ 10.82 (s, 1H), 9.33 (s, 1H), 7.27 – 7.15 (m, 3H), 6.93 – 6.78 (m, 3H), 6.69 (dd, *J* = 21.8, 8.6 Hz, 3H), 6.57 (dd, *J* = 15.2, 2.4 Hz, 1H), 6.51 – 6.39 (m, 3H), 6.38 – 6.28 (m, 2H), 5.85 (d, *J* = 7.6 Hz, 1H), 4.42 – 4.20 (m, 4H), 3.65 – 3.55 (m, 3H), 2.92 (s, 4H), 2.83 – 2.68 (m, 2H), 2.67 – 2.57 (m, 5H), 2.25 (s, 2H), 2.19 – 2.01 (m, 2H), 1.99 – 1.75 (m, 4H), 1.75 – 1.49 (m, 2H). | D | 704.4 | 704.5 |
| **A31** | $^1$H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.40 (s, 1H), 7.81 (s, 2H), 7.14-7.12 (m, 3H), 6.75 (s, 2H), 6.66-6.59 (m, 3H), 6.38-6.36 (m, 2H), 6.27-6.25 (m, 2H), 5.15-5.10 (m, 1H), 4.32-4.29 (m, 1H), 4.18-4.14 (m, 2H), 4.08 (s, 4H), 3.75-3.50 | B | 794.4 | 794.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| | (m, 2H), 3.01 (s, 4H), 1.52-1.38 (m, 13H), 0.98-0.95 (m, 4H). | | | |
| **A32** | $^{1}$H NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.31 (s, 1H), 7.92 (s, 2H), 7.15-7.14 (m, 3H), 6.79-6.77 (m, 2H), 6.64-6.62 (d, J = 8.4 Hz, 1H), 6.34-6.25 (m, 4H), 6.18 (d, J = 8.0 Hz, 2H), 5.18-5.13 (m, 1H), 5.03 (s, 2H), 4.77 (s, 2H), 4.33-4.30 (m, 1H), 4.19-4.13 (m, 2H), 3.50-3.46 (m, 1H), 3.36-3.32 (m, 2H), 3.16-2.90 (m, 5H), 2.75-2.69 (m, 4H), 2.08-2.07 (m, 1H), 2.00-1.92 (m, 2H), 1.76-1.73 (m, 2H), 1.23 (s, 2H). | B | 812.4 | 814.5 |
| **A33** | $^{1}$H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.32 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.11 – 6.94 (m, 2H), 6.76 – 6.57 (m, 4H), 6.40 (dd, *J* = 20.2, 7.6 Hz, 3H), 6.32 – 6.19 (m, 3H), 5.11 – 4.95 (m, 1H), 4.43 – 4.21 (m, 3H), 4.19 – 4.05 (m, 3H), 4.04 – 3.91 (m, 1H), 3.82 (d, *J* = 10.8 Hz, 1H), 3.56 (s, 5H), 3.50 – 3.42 (m, 1H), 3.18 (s, 1H), 3.03 – 2.82 (m, 3H), 2.80 – 2.69 (m, 1H), 2.64 – 2.53 (m, 3H), 2.47 – 2.31 (m, 2H), 2.27 – 2.03 (m, 3H), 1.95 (s, 1H), 1.85 – 1.49 (m, 5H). | C | 784.4 | 784.4 |
| **A34** | $^{1}$H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.29 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.09 – 6.98 (m, 2H), 6.73 – 6.61 (m, 4H), 6.40 (dd, *J* = 19.8, 8.0 Hz, 3H), 6.32 – 6.23 (m, 3H), 5.03 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.40 – 4.21 (m, 3H), 4.19 – 4.06 (m, 3H), 3.97 (dd, *J* = 19.2, 9.4 Hz, 1H), 3.83 (d, *J* = 11.2 Hz, 1H), 3.62 – 3.52 (m, 5H), 3.51 – 3.43 (m, 1H), 3.22 – 3.11 (m, 1H), 2.98 – 2.83 (m, 3H), 2.75 (t, *J* = 11.2 Hz, 1H), 2.60 – 2.52 (m, 3H), 2.46 – 2.30 (m, 2H), 2.22 – 2.05 (m, 3H), 2.01 – 1.85 (m, 2H), 1.79 – 1.60 (m, 4H). | C | 784.4 | 784.4 |
| **A35** | $^{1}$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H), | B | 756.4 | 756.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H). | | | |
| **A36** | $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H), 7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H). | B | 756.4 | 756.5 |
| **A37** | $^1$H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.29 (s, 1H), 7.20 – 7.10 (m, 4H), 7.01 (d, J = 8.4 Hz, 1H), 6.81 – 6.70 (m, 2H), 6.70 – 6.54 (m, 3H), 6.41 – 6.24 (m, 4H), 5.08 – 4.98 (m, 1H), 4.38 – 4.07 (m, 6H), 4.02 – 3.91 (m, 1H), 3.81 (d, J = 10.4 Hz, 1H), 3.54 – 3.49 (m, 1H), 3.17 – 3.11 (m, 1H), 3.03 – 2.83 (m, 7H), 2.72 (t, J = 11.6 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.47 – 2.33 (m, 4H), 2.11 (t, J = 11.4 Hz, 1H), 2.00 – 1.87 (m, 3H), 1.79 – 1.58 (m, 3H), 1.55 – 1.36 (m, 4H). | F | 794.4 | 794.4 |
| **A38** | $^1$H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.31 (s, 1H), 7.80 (s, 2H), 7.14(s, 3H), 6.76-6.74 (m, 2H), 6.63 (d, J = 8.4 Hz, 1H), 6.35-6.26 (m, 4H), 6.09(d, J = 5.2 Hz, 2H), 5.15-5.11 (m, 1H), 4.32-4.28 (m, 1H), 4.19-4.14 (m, 2H), 4.08 (s, 4H), 3.61 (s, 2H), 3.50-3.44 (m, 7H), 2.91-2.89 (m, 1H), 2.67-2.53 (m, 2H), 2.09-2.07 (m, 1H), 2.04-1.65 (m, 4H), 1.24 (s, 2H). | C | 766.4 | 766.5 |
| **A39** | $^1$H NMR (400 MHz, MeOD-d4) δ 8.51 (s, 1H), 7.75 (s, 2H), 7.12-7.09 | C | 766.4 | 766.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^{+}$ | Found. $(M+H)^{+}$ |
|---|---|---|---|---|
| | (m, 2H), 6.72-6.67 (m, 5H), 6.47 (d, J = 8.4 Hz, 2H), 6.35-6.29 (m, 2H), 5.15-5.10 (m, 1H), 4.42 (t, J = 10.8 Hz, 1H), 4.19-4.15 (m, 5H), 4.00 (s, 2H), 3.76 (s, 2H), 3.53-3.50 (m, 3H), 3.11-2.97 (m, 4H), 2.84-2.74 (m, 2H), 2.17-2.15 (m, 1H), 1.90-1.87 (m, 4H), 1.30 (s, 2H). | | | |
| **A40** | $^{1}$H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.27 (s, 1H), 7.88 (s, 2H), 7.15-7.13 (m, 3H), 6.78-6.74 (m, 2H), 6.66-6.60 (s, 3H), 6.39-6.36 (m, 2H), 6.30-6.26 (m, 2H), 5.15-5.11 (m, 1H), 4.33-4.30 (m, 1H), 4.19-4.16 (m, 2H), 4.09 (s, 4H), 3.61 (s, 2H), 3.52-3.45 (m, 4H), 3.03-3.01 (m, 4H), 1.53-1.47 (m, 7H), 1.73-1.38 (m, 6H). | B | 794.4 | 794.5 |
| **A41** | $^{1}$H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.36 (s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 3.6 Hz, 1H), 7.15-7.13 (m, 3H), 6.77-6.76 (m, 2H), 6.66-6.59 (m, 3H), 6.38-6.36 (m, 2H), 6.31-6.26 (m, 2H), 5.14-5.11 (m, 1H), 5.01-4.98 (m, 2H), 4.71 (d, J = 7.2 Hz, 2H), 4.47-4.43 (m, 1H), 4.34-4.30 (m, 2H), 4.20-4.16 (m, 2H), 3.53-3.48 (m, 3H), 3.25 (s, 3H). 3.01-2.98 (m, 4H), 2.97-2.89 (m, 1H), 2.67-2.59 (m, 1H), 2.47-2.41 (m, 2H), 2.03-1.97 (m, 1H), 1.48-1.46 (m, 8H). | C | 780.4 | 780.6 |

| Compound No | [1]HNMR | LCMS method | Calcd. (M+H)+ | Found. (M+H)+ |
|---|---|---|---|---|
| **A42** | [1]H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.27 (s, 1H), 7.74 (s, 1H), 7.60 (s, 1H), 7.15-7.13 (m, 3H), 6.78-6.76 (m, 2H), 6.66-6.61 (m, 3H), 6.39-6.37 (m, 2H), 6.31-6.26 (m, 2H), 5.14-5.09 (m, 1H), 5.00-4.97 (m, 2H), 4.76 (d, J = 7.6 Hz, 2H), 4.49-4.44 (m, 1H), 4.36-4.30 (m, 2H), 4.20-4.17 (m, 2H), 3.54-3.50 (m, 1H), 3.02 (s, 4H). 2.98-2.87 (m, 2H), 2.67-2.59 (m, 2H), 2.50-2.41 (m, 1H), 2.02-1.99 (m, 2H), 1.62-1.38 (m, 8H), 1.27-1.24 (m, 3H). | C | 780.4 | 780.6 |
| **A43** | [1]H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.30 (s, 2H), 7.92 (s, 2H), 7.15-7.13 (m, 3H), 6.77-6.75 (m, 2H), 6.66-6.60 (m, 3H), 6.38-6.36(m, 2H), 6.30-6.25 (m, 2H), 5.67-5.61 (m, 1H), 5.16 (s, 2H), 4.77 (s, 2H), 4.33-4.31 (m, 1H), 4.18-4.16 (m, 2H), 3.52-3.49 (m, 2H), 3.23 (s, 4H), 3.00-2.88 (m, 6H), 2.61-2.56 (m, 3H). 2.17-2.08 (m, 1H), 1.49-1.46 (m, 8H). | C | 840.4 | 840.6 |
| **A44** | [1]H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 7.83 (s, 2H), 7.15-7.13 (m, 3H), 6.77-6.74 (m, 2H), 6.65-6.63 (m, 1H), 6.36-6.25 (m, 4H), 6.12-6.10 (d, J = 8.4 Hz, 2H), 5.16-5.11 (m, 1H), 4.35-4.29 (m, 1H), 4.19-4.14 (m, 6H), 4.77 (s, 2H), 3.51-3.44 (m, 8H), 2.89-2.86 (m, 1H), 2.64-2.55 (m, 2H). 2.07-2.05 (m, 1H), 1.72-1.67 (m, 4H). 1.24-0.93 (m, 2H). | C | 766.4 | 766.6 |
| **A45** | [1]H NMR (400 MHz, DMSO-d6) δ 11.03 (s, 1H), 10.48 (s, 1H), 9.32 (s, 1H), 7.76 (d, J = 11.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.15-7.10 (m, 3H), 6.77-6.63 (m, 2H), 6.62-6.57 (m, 3H), 6.41-6.38 (m, 2H), 6.30-6.26 (m, 3H), 5.14-5.12 (m, 1H), 4.88 (d, J = 5.6 Hz, 2H), 4.78 (m, 2H), | B | 798.4 | 798.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^{+}$ | Found. $(M+H)^{+}$ |
|---|---|---|---|---|
| | 4.50-4.45 (m, 3H), 4.36-4.29 (m, 2H), 4.20-4.18 (m, 2H). 4.09-4.04 (m, 3H), 3.93-3.90 (m, 1H), 3.54-3.49 (m, 2H). 3.06-2.92 (m, 4H), 2.18-2.09 (m, 1H), 1.96-1.87 (m, 1H), 2.07-1.80 (m, 5H). | | | |
| **A46** | $^{1}$H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.62 (s, 1H), 7.91 (d, J = 3.6 Hz, 2H), 7.15-7.13 (m, 3H), 6.76-6.74 (m, 2H), 6.63(d, J = 8.4 Hz, 1H), 6.35-6.26 (m, 4H), 6.10 (d, J = 8.4 Hz, 2H), 5.17-5.13 (m, 1H), 5.07 (s, 2H), 4.78 (s, 2H), 4.32-4.19 (m, 1H), 4.18-4.14 (m, 2H), 3.47-3.43 (m, 5H). 3.22(s, 3H), 2.91-2.88 (m, 1H), 2.67-2.58 (m, 2H), 2.46-2.43 (m, 3H), 2.11-2.08 (m, 1H), 1.73-1.71 (m, 4H). | B | 812.4 | 812.5 |
| **A47** | $^{1}$H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.36 (s, 1H), 7.91 (d, J = 3.6 Hz, 2H), 7.15-7.13 (m, 3H), 6.76-6.74 (m, 2H), 6.62(d, J = 8.0 Hz, 1H), 6.34-6.26 (m, 4H), 6.10 (d, J = 8.4 Hz, 2H), 5.17-5.12 (m, 1H), 5.07 (s, 2H), 4.78 (s, 2H), 4.33-4.31 (m, 1H), 4.18-4.14 (m, 2H), 3.50-3.41 (m, 4H). 3.22 (s, 4H), 2.87-2.80 (m, 1H), 2.63-2.57 (m, 2H), 2.43-2.40 (m, 4H), 1.72 (s, 4H). | B | 766.4 | 766.5 |
| **A48** | $^{1}$H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.25 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 6.0Hz, 1H), 7.15-7.13 (m, 3H), 6.76-6.74 (m, 2H), 6.63 (d, J = 8.4 Hz, 1H), 6.35-6.25 (m, 4H), 6.10 (d, J = 8.4 Hz, 2H), 5.09-5.07 (m, 1H), 4.98 (d, J = 10.4 Hz, 2H), 4.71 (d, J = 7.6 Hz, 2H), 4.47-4.43 (m, 1H), 4.34-4.30 (m, 2H), 4.18-4.141 (m, 2H), 3.50-3.42 (m, 7H), 3.21-3.17 (m, 2H), 2.93-2.89 (m, 1H), 2.67-2.57 (m, 2H), 2.43-2.39 (m, 2H), 2.12-1.97 (m, 1H), 1.72 (s, 4H). | C | 798.4 | 798.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| A49 | $^{1}$H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.33 (s, 1H), 7.68 (d, J = 9.6 Hz, 1H), 7.56 (d, J = 6.4 Hz, 1H), 7.15-7.13 (m, 3H), 6.76-6.74 (m, 2H), 6.63 (d, J = 8.4 Hz, 1H), 6.35-6.26 (m, 4H), 6.12-6.10 (m, 2H), 5.11-5.07 (m, 1H), 5.01-4.98 (m, 2H), 4.71 (m, 2H), 4.47-4.43 (m, 1H), 4.34-4.29 (m, 2H), 4.21-4.14 (m, 2H), 3.50-3.47 (m, 4H), 3.20 (s, 3H), 2.90-2.87 (m, 1H), 2.71-2.63 (m, 2H), 2.43-2.38 (m, 4H), 2.02-1.97 (m, 1H), 1.72 (s, 4H). | C | 752.4 | 752.4 |
| A50 | $^{1}$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.32 (s, 1H), 7.20 – 7.10 (m, 4H), 7.00 (d, J = 8.6 Hz, 1H), 6.80 – 6.72 (m, 2H), 6.70 – 6.56 (m, 3H), 6.42 – 6.23 (m, 4H), 5.08 – 4.97 (m, 1H), 4.36 – 4.07 (m, 6H), 4.01 – 3.91 (m, 1H), 3.80 (d, J = 9.8 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.16 – 3.12 (m, 1H), 3.01 – 2.95 (m, 2H), 2.94 – 2.83 (m, 5H), 2.75 – 2.69 (m, 1H), 2.62 – 2.52 (m, 2H), 2.44 – 2.34 (m, 3H), 2.18 – 2.05 (m, 1H), 2.01 – 1.86 (m, 3H), 1.80 – 1.57 (m, 3H), 1.56 – 1.34 (m, 4H). | F | 794.4 | 794.5 |
| A51 | $^{1}$H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.26 (s, 1H), 7.21 – 7.08 (m, 3H), 6.85 – 6.71 (m, 3H), 6.68 – 6.56 (m, 3H), 6.54 – 6.45 (m, 1H), 6.43 – 6.24 (m, 5H), 5.79 (d, J = 7.6 Hz, 1H), 4.35 – 4.15 (m, 4H), 3.53 – 3.50 (m, 1H), 3.01 – 2.78 (m, 9H), 2.62 – 2.52 (m, 2H), 2.47 – 2.38 (m, 6H), 2.12 – 2.04 (m, 1H), 1.94 – 1.81 (m, 3H), 1.64 – 1.37 (m, 6H). | F | 744.4 | 744.4 |
| A52 | $^{1}$H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.26 (s, 1H), 7.17 – 7.11 (m, 3H), 6.84 – 6.73 (m, 3H), 6.68 – 6.57 (m, 3H), 6.55 – 6.45 (m, 1H), 6.43 – 6.34 (m, 3H), 6.32 – 6.24 (m, 2H), 5.79 (d, J = 7.4 Hz, 1H), 4.35 – 4.16 (m, 4H), 3.52 – 3.49 (m, 1H), 3.00 – | F | 744.4 | 744.4 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 2.96 (m, 2H), 2.91 – 2.86 (m, 2H), 2.85 – 2.78 (m, 4H), 2.75 – 2.69 (m, 1H), 2.62 – 2.53 (m, 2H), 2.47 – 2.43 (m, 4H), 2.38 (d, J = 7.0 Hz, 2H), 2.13 – 2.04 (m, 1H), 1.95 – 1.81 (m, 3H), 1.65 – 1.59 (m, 2H), 1.52 – 1.37 (m, 4H). | | | |
| **A53** | $^{1}$H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.21 – 7.11 (m, 3H), 7.03 (s, 1H), 6.94 (s, 1H), 6.76 (s, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.38 – 6.25 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.10 – 4.95 (m, 1H), 4.32 – 4.12 (m, 6H), 3.98 – 3.78 (m, 3H), 3.39 – 3.34 (m, 4H), 3.18 – 3.04 (m, 2H), 2.96 – 2.85 (m, 3H), 2.80 – 2.71 (m, 1H), 2.61 – 2.54 (m, 1H), 2.41 – 2.29 (m, 1H), 2.21 – 2.05 (m, 3H), 2.02 – 1.92 (m, 1H), 1.87 – 1.79 (m, 2H), 1.68 (d, J = 9.8 Hz, 3H), 1.56 – 1.39 (m, 3H), 0.99 – 0.80 (m, 2H). | C | 794.4 | 794.5 |
| **A54** | $^{1}$H NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.64 (s, 1H), 9.27 (s, 1H), 7.97 (s, 1H), 7.15-7.13 (m, 3H), 6.78-6.75 (m, 2H), 6.71-6.64 (m, 3H), 6.42-6.40 (m, 2H), 6.32-6.30 (m, 2H), 5.16-5.14 (m, 1H), 4.96 (s, 2H), 4.88 (s, 2H), 4.33-4.30 (m, 3H), 4.21-4.18 (m, 2H), 3.38-3.33 (m, 3H), 3.27-3.18 (m, 2H), 3.11-3.04 (m, 4H), 2.87-2.80 (m, 1H), 2.77-2.61 (m, 2H).. 2.15-2.07 (m, 1H), 1.87-1.81 (m, 2H), 1.69-1.66 (m, 4H), 1.47 (s, 2H). | C | 840.4 | 840.6 |
| **A55** | $^{1}$H NMR (400 MHz, DMSO-d6) δ 11.02 (s, 1H), 9.23 (s, 1H), 7.91 (d, J = 2.0 Hz, 2H), 7.15-7.13 (m, 3H), 6.76-6.72 (m, 2H), 6.64-6.60 (m, 3H), 6.36 (d, J = 8.8 Hz, 2H), 6.27-6.25 (m, 2H), 5.17-5.13 (m, 1H), 4.97 (s, 2H), 4.74 (s, 2H), 4.32 (d, J = 10.8 Hz, 1H), 4.19-4.16 (m, 2H), 3.52-3.49 (m, 1H), 3.82-3.78 (m, 2H). 3.01 (s, 4H), 2.96 (s, 4H), 2.91-2.87 (m, | B | 812.4 | 812.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| | 1H), 2.66-2.58 (m, 2H), 2.08-2.06 (m, 1H), 1.75-1.72 (m, 4H). | | | |
| **A56** | $^1$H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.25 (s, 1H), 8.24 (s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 6.4 Hz, 1H), 7.15-7.13 (m, 3H), 6.77-6.73 (m, 2H), 6.66-6.60 (m, 3H), 6.38-6.36 (m, 2H), 6.31-6.25 (m, 3H), 5.12-5.09 (m, 1H), 4.89-4.85 (m, 2H), 4.70-4.65 (m, 2H), 4.47-4.45 (m, 1H), 4.34-4.29 (m, 2H), 4.19-4.16 (m, 2H), 3.54-3.48 (m, 2H). 3.15-3.01 (m, 4H). 2.97-2.95 (m, 4H), 2.93-2.87 (m, 1H), 2.61-2.54 (m, 2H), 2.43-2.38 (m, 1H), 2.08-1.97 (m, 1H), 1.75-1.72 (m, 4H). | B | 798.4 | 798.4 |
| **A57** | $^1$H NMR (400 MHz, DMSO-d6) δ 11.14 (s, 1H), 9.57 (s, 1H), 7.98-7.96 (m, 2H), 7.14-7.11 (m, 3H), 6.77-6.65 (m, 5H), 6.45-6.43 (m, 2H), 6.31-6.26 (m, 2H), 5.24-5.15 (m, 2H), 5.04-4.81 (m, 3H), 4.42-4.30 (m, 2H), 4.21 (s, 2H), 3.26-3.23 (s, 3H), 3.07 (s, 5H), 2.95-2.93 (m, 1H), 2.67-2.56 (m, 2H), 2.13-2.08 (m, 1H), 1.88-1.67 (m, 5H), 1.54-1.41 (m, 6H), 1.21 (s, 1H). | C | 808.4 | 808.5 |
| **A58** | $^1$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.17 – 7.11 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.80 – 6.71 (m, 2H), 6.67 – 6.57 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.24 (m, 2H), 5.08 – 4.98 (m, 1H), 4.34 – 4.13 (m, 6H), 3.94 – 3.76 (m, 2H), 3.54 – 3.47 (m, 1H), 3.17 – 3.09 (m, 1H), 3.02 – 2.95 (m, 2H), 2.93 – 2.84 (m, 5H), 2.78 – 2.67 (m, 1H), 2.61 – 2.53 (m, 2H), 2.43 – 2.34 (m, 3H), 2.10 (t, J = 10.6 Hz, 1H), 1.98 – 1.87 (m, 3H), 1.72 (t, J = 10.6 Hz, 1H), 1.66 – 1.59 (m, 2H), 1.55 – 1.47 (m, 2H), 1.41 (t, J = 9.8 Hz, 2H). | E | 794.4 | 794.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| **A59** | 1H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.28 (s, 1H), 7.18 – 7.09 (m, 3H), 7.03 (s, 1H), 6.92 (s, 1H), 6.80 – 6.71 (m, 2H), 6.69 – 6.55 (m, 3H), 6.42 – 6.23 (m, 4H), 5.09 – 4.95 (m, 1H), 4.35 – 4.13 (m, 6H), 3.92 – 3.76 (m, 2H), 3.53 – 3.50 (m, 1H), 3.15 – 3.13 (m, 1H), 3.00 – 2.86 (m, 7H), 2.79 – 2.70 (m, 1H), 2.61 – 2.55 (m, 2H), 2.44 – 2.37 (m, 3H), 2.10 (t, J = 10.6 Hz, 1H), 2.02 – 1.87 (m, 3H), 1.75 – 1.59 (m, 3H), 1.54 – 1.37 (m, 4H). | F | 794.4 | 794.5 |
| **A60** | 1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.26 (s, 1H), 7.68 (d, J = 10.4 Hz, 1H), 7.56 (d, J = 5.2 Hz, 1H), 7.15-7.13 (m, 3H), 6.77-6.75 (m, 2H), 6.66-6.64 (m, 1H), 6.58 (d, J = 8.8 Hz, 2H), 6.35 (d, J = 8.4 Hz, 2H), 6.30-6.25 (m, 2H), 5.16-5.09 (m, 2H), 5.01-4.95 (m, 1H), 4.72 (d, J = 8.4 Hz, 2H), 4.49-4.43 (m, 1H), 4.35-4.30 (m, 2H), 4.20-4.15 (m, 2H), 3.73-3.65 (m, 4H), 3.52-3.49 (m, 2H), 3.26 (s, 3H), 2.98-2.88 (m, 6H), 2.74-2.62 (m, 4H), 2.03-1.99 (m, 1H), 1.45-1.36 (m, 8H). | B | 824.4 | 824.5 |
| **A61** | DMSO-d6: δ 10.93 (s, 1H), 9.31 (s, 1H), 8.13 (s, 1H), 7.29 – 7.16 (m, 4H), 6.99 (s, 1H), 6.89 – 6.81 (m, 2H), 6.75 – 6.64 (m, 2H), 6.61 – 6.47 (m, 1H), 6.36 – 6.22 (m, 2H), 5.10 – 4.96 (m, 1H), 4.41 – 4.07 (m, 9H), 4.05 – 3.50 (m, 4H), 3.24 – 3.02 (m, 2H), 2.99 – 2.83 (m, 2H), 2.77 – 2.54 (m, 4H), 2.42 – 2.30 (m, 1H), 2.27 – 1.91 (m, 3H), 1.87 – 1.64 (m, 3H), 1.09 (s, 2H). | E | 755.4 | 755.4 |
| **A62** | $^{1}$H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.22 – 7.01 (m, 6H), 6.81 – 6.73 (m, 2H), 6.63 (dd, *J* = 20.8, 8.4 Hz, 3H), 6.38 (d, *J* = 8.6 Hz, 2H), 6.33 – 6.24 (m, 2H), 5.04 (dd, *J* = | B | 726.4 | 726.4 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 13.4, 5.2 Hz, 1H), 4.41 – 4.13 (m, 6H), 3.62 – 3.47 (m, 4H), 3.30 – 3.22 (m, 5H), 2.63 – 2.53 (m, 5H), 2.19 (d, *J* = 6.6 Hz, 2H), 2.07 – 1.87 (m, 2H), 1.84 – 1.49 (m, 4H). | | | |
| **A63** | 1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.14 (s, 3H), 7.04 (s, 1H), 6.94 (s, 1H), 6.76 (s, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.36 – 6.24 (m, 4H), 6.09 (d, J = 8.0 Hz, 2H), 5.09 – 4.98 (m, 1H), 4.38 – 4.20 (m, 4H), 4.21 – 4.13 (m, 3H), 3.93 – 3.76 (m, 4H), 3.41 – 3.35 (m, 4H), 3.19 – 3.14 (m, 1H), 2.93 – 2.85 (m, 3H), 2.80 – 2.69 (m, 2H), 2.62 – 2.56 (m, 1H), 2.41 – 2.34 (m, 1H), 2.13 – 2.06 (m, 2H), 2.06 – 1.93 (m, 2H), 1.86 – 1.78 (m, 2H), 1.70 – 1.64 (m, 2H), 1.47 – 1.39 (m, 2H), 0.97 – 0.85 (m, 2H). | C | 794.4 | 794.5 |
| **A64** | DMSO-d6: δ 10.93 (s, 1H), 8.24 (s, 1H), 7.26 (s, 1H), 7.22 – 7.12 (m, 4H), 7.01 (d, J = 8.4 Hz, 1H), 6.89 – 6.79 (m, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.51 (d, J = 8.8 Hz, 1H), 6.35 – 6.22 (m, 2H), 5.03 (dd, 1H), 4.43 – 4.04 (m, 8H), 4.02 – 3.93 (m, 1H), 3.82 (d, J = 10.4 Hz, 1H), 3.57 – 3.52 (m, 1H), 3.20 – 3.16 (m, 1H), 2.99 – 2.81 (m, 3H), 2.79 – 2.55 (m, 4H), 2.44 – 2.30 (m, 1H), 2.25 – 2.03 (m, 3H), 2.00 – 1.88 (m, 1H), 1.82 – 1.64 (m, 4H), 1.12 – 0.96 (m, 2H). | E | 755.4 | 755.4 |
| **A65** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.43 (s, 1H), 7.28 – 7.11 (m, 5H), 7.05 – 6.94 (m, 1H), 6.88 – 6.73 (m, 2H), 6.70 – 6.57 (m, 2H), 6.54 – 6.44 (m, 1H), 6.35 – 6.20 (m, 2H), 5.03 (d, J = 13.2 Hz, 1H), 4.35 – 4.05 (m, 6H), 4.01 – 3.90 (m, 1H), 3.83 – 3.74 (m, 1H), 3.57 – 3.45 (m, 2H), 3.27 – 3.22 (m, 3H), 3.19 – 3.06 (m, 2H), 2.94 – 2.81 (m, 3H), 2.76 – 2.62 (m, 2H), 2.43 – 2.34 (m, 3H), 2.18 – 2.04 (m, 1H), 1.99 – 1.87 (m, 3H), | C | 795.4 | 795.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 1.80 – 1.66 (m, 1H), 1.54 (s, 2H), 1.42 (s, 4H). | | | |
| **A66** | DMSO-d6: δ 10.93 (s, 1H), 8.27 (s, 2H), 7.28 – 7.14 (m, 5H), 7.00 (d, J = 8.4 Hz, 1H), 6.88 – 6.77 (m, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.8 Hz, 1H), 6.36 – 6.23 (m, 2H), 5.07 – 4.96 (m, 1H), 4.39 – 4.16 (m, 5H), 4.09 (d, J = 16.4 Hz, 1H), 4.03 – 3.92 (m, 1H), 3.87 – 3.77 (m, 1H), 3.60 – 3.49 (m, 2H), 3.26 – 3.09 (m, 5H), 2.96 – 2.84 (m, 3H), 2.75 – 2.66 (m, 1H), 2.63 – 2.55 (m, 1H), 2.44 – 2.32 (m, 3H), 2.18 – 2.06 (m, 1H), 2.02 – 1.89 (m, 3H), 1.81 – 1.68 (m, 1H), 1.60 – 1.50 (m, 2H), 1.48 – 1.35 (m, 4H). | E | 795.4 | 795.5 |
| **A67** | 1HNMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.38 (s, 1H), 7.51 (d, J=8 Hz 1H), 7.24-7.05 (m, 7H), 6.84 (s, 2H), 6.67-6.65 (m, 2H), 6.52-6.50 (m, 1H), 6.31-6.28 (m, 2H), 5.05-5.02 (m, 1H), 4.34-4.18 (m, 6H), 3.25 (s, 9H), 3.09-2.86 (m, 3H), 2.74-2.34 (m, 3H), 1.95-1.93 (m, 4H), 1.54-1.42 (m, 7H). | B | 767.4 | 767.5 |
| **A68** | DMSO-d6: δ 10.95 (s, 1H), 9.65 (s, 1H), 9.35 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.33 – 7.12 (m, 6H), 6.97 – 6.85 (m, 2H), 6.80 – 6.44 (m, 4H), 6.38 – 6.24 (m, 2H), 5.06 (dd, 1H), 4.41 – 4.20 (m, 5H), 4.08 – 3.95 (m, 2H), 3.66 – 3.49 (m, 3H), 3.28 – 3.25 (m, 2H), 3.21 – 3.03 (m, 5H), 2.99 – 2.84 (m, 1H), 2.79 – 2.55 (m, 2H), 2.45 – 2.28 (m, 2H), 2.13 – 1.90 (m, 3H), 1.70 – 1.40 (m, 6H). | B | 767.4 | 767.5 |
| **A69** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.34 (s, 1H), 7.28 – 7.14 (m, 5H), 7.01 (d, J = 8.2 Hz, 1H), 6.91 – 6.78 (m, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.8 Hz, 1H), 6.38 – 6.23 (m, 2H), 5.09 – 4.97 (m, 1H), 4.37 – 4.08 (m, 8H), 4.03 – 3.91 (m, | E | 755.4 | 755.4 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 1H), 3.82 (d, J = 9.8 Hz, 1H), 3.56 – 3.50 (m, 1H), 3.20 – 3.14 (m, 1H), 2.97 – 2.85 (m, 3H), 2.77 – 2.58 (m, 4H), 2.42 – 2.33 (m, 1H), 2.22 – 2.05 (m, 3H), 2.00 – 1.84 (m, 1H), 1.73 (d, J = 10.0 Hz, 4H), 1.03 (d, J = 11.6 Hz, 2H). | | | |
| **A70** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.31 (s, 1H), 7.29 – 7.14 (m, 4H), 7.04 (s, 1H), 6.93 (s, 1H), 6.89 – 6.80 (m, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.51 (d, J = 8.8 Hz, 1H), 6.36 – 6.24 (m, 2H), 5.08 – 4.97 (m, 1H), 4.34 – 4.05 (m, 8H), 3.94 – 3.76 (m, 2H), 3.56 – 3.50 (m, 1H), 3.20 – 3.14 (m, 1H), 2.98 – 2.59 (m, 7H), 2.38 – 2.27 (m, 1H), 2.23 – 2.03 (m, 3H), 2.01 – 1.89 (m, 1H), 1.81 – 1.63 (m, 4H), 1.12 – 0.93 (m, 2H). | F | 755.4 | 755.4 |
| **A71** | 1H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 8.20 (s, 1H), 7.44 (s, 1H), 7.21 – 7.08 (m, 3H), 7.00 (s, 1H), 6.82 – 6.54 (m, 5H), 6.44 – 6.20 (m, 4H), 5.12 – 5.02 (m, 1H), 4.50 – 4.40 (m, 2H), 4.38 – 4.27 (m, 2H), 4.25 – 4.14 (m, 3H), 3.53 – 3.50 (m, 1H), 3.01 – 2.95 (m, 2H), 2.93 – 2.85 (m, 3H), 2.79 (d, J = 9.4 Hz, 2H), 2.64 – 2.54 (m, 1H), 2.45 – 2.30 (m, 4H), 2.02 – 1.84 (m, 7H), 1.71 – 1.57 (m, 4H), 1.55 – 1.46 (m, 2H), 1.41 (t, J = 9.8 Hz, 2H). | F | 793.4 | 793.5 |
| **A72** | $^{1}$H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 9.33 (s, 1H), 7.24 – 7.16 (m, 3H), 7.04 (t, *J* = 8.6 Hz, 1H), 6.86 – 6.79 (m, 2H), 6.70 (dd, *J* = 20.4, 8.4 Hz, 3H), 6.55 – 6.41 (m, 4H), 6.39 – 6.30 (m, 2H), 6.07 (d, *J* = 7.4 Hz, 1H), 4.48 – 4.31 (m, 2H), 4.30 – 4.18 (m, 2H), 3.63 – 3.54 (m, 4H), 3.13 – 2.85 (m, 2H), 2.87 – 2.63 (m, 3H), 2.42 – 1.86 (m, 8H), 1.88 – 1.62 (m, 8H). | B | 703.4 | 703.4 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| **A73** | 1H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 8.30 (s, 1H), 7.17 – 7.07 (m, 4H), 7.01 – 6.87 (m, 2H), 6.79 – 6.73 (m, 2H), 6.67 – 6.58 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.24 (m, 2H), 5.37 – 5.29 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.17 (t, J = 6.8 Hz, 2H), 3.52 – 3.50 (m, 1H), 3.32 (s, 3H), 3.01 – 2.95 (m, 2H), 2.94 – 2.86 (m, 5H), 2.73 – 2.58 (m, 2H), 2.44 – 2.34 (m, 4H), 2.02 – 1.88 (m, 5H), 1.72 – 1.60 (m, 6H), 1.54 – 1.47 (m, 2H), 1.45 – 1.36 (m, 2H). | E | 780.4 | 780.4 |
| **A74** | 1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.24 (s, 1H), 7.24 – 6.93 (m, 5H), 6.71 – 6.20 (m, 8H), 5.03 (s, 1H), 4.63 (s, 1H), 4.36 – 3.99 (m, 6H), 3.90 – 3.42 (m, 6H), 3.13 – 2.85 (m, 7H), 2.78 – 2.61 (m, 2H), 2.17 – 1.67 (m, 6H), 1.61 – 1.08 (m, 5H). | F | 784.4 | 784.4 |
| **A75** | 1H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 8.30 (s, 2H), 7.18 – 7.08 (m, 3H), 6.97 (t, J = 8.8 Hz, 1H), 6.81 – 6.71 (m, 2H), 6.67 – 6.57 (m, 3H), 6.47 – 6.34 (m, 4H), 6.32 – 6.24 (m, 2H), 5.99 (d, J = 7.6 Hz, 1H), 4.38 – 4.24 (m, 2H), 4.21 – 4.13 (m, 2H), 3.53 – 3.50 (m, 1H), 3.01 – 2.94 (m, 2H), 2.88 (d, J = 7.2 Hz, 4H), 2.78 – 2.67 (m, 1H), 2.61 – 2.52 (m, 2H), 2.37 (d, J = 6.4 Hz, 2H), 2.12 – 2.04 (m, 1H), 2.01 – 1.85 (m, 5H), 1.65 – 1.57 (m, 6H), 1.53 – 1.46 (m, 2H), 1.39 (t, J = 9.8 Hz, 2H). | E | 743.4 | 743.4 |
| **A76** | 1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.25 (s, 1H), 7.21 – 7.00 (m, 5H), 6.69 – 6.16 (m, 8H), 5.03 (dd, J = 12.8, 4.8 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.39 – 4.22 (m, 3H), 4.14 – 3.94 (m, 3H), 3.83 (d, J = 11.2 Hz, 1H), 3.53 (M, 3H), 3.01 (M, 4H), 2.96 – 2.82 (m, 3H), 2.78 – 2.58 (m, 3H), 2.42 – 2.30 (m, 1H), 2.16 (M, | F | 784.4 | 784.4 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 3H), 1.80 (M, 5H), 1.33 – 1.10 (m, 3H). | | | |
| **A77** | DMSO-d6:δ 10.93 (s, 1H), 9.24 (s, 1H), 7.13 – 7.03 (m, 4H), 6.94 (s, 1H), 6.72 – 6.65 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.49 (d, J = 8.2 Hz, 1H), 6.36 (d, J = 8.0 Hz, 1H), 6.31 – 6.23 (m, 2H), 6.18 (s, 1H), 5.03 (dd, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.37 – 4.22 (m, 3H), 4.19 – 4.00 (m, 2H), 3.97 – 3.77 (m, 2H), 3.68 – 3.54 (m, 2H), 3.50 – 3.40 (m, 1H), 3.23 – 3.12 (m, 1H), 3.02 (s, 3H), 2.98 – 2.79 (m, 3H), 2.75 – 2.55 (m, 4H), 2.43 – 2.04 (m, 4H), 1.99 – 1.88 (m, 1H), 1.83 – 1.60 (m, 4H), 1.32 – 1.11 (m, 2H). | E | 784.4 | 784.4 |
| **A78** | $^{1}$H NMR (400 MHz, DMSO) δ 11.19 (s, 1H), 9.34 (s, 1H), 7.96 (d, *J* = 18.8 Hz, 2H), 7.25 – 7.15 (m, 3H), 6.85 – 6.78 (m, 2H), 6.71 (dd, *J* = 17.4, 8.4 Hz, 3H), 6.45 (d, *J* = 8.6 Hz, 2H), 6.38 – 6.31 (m, 2H), 5.22 (dd, *J* = 12.8, 5.4 Hz, 1H), 5.12 (s, 2H), 4.82 (s, 2H), 4.39 (t, *J* = 11.2 Hz, 1H), 4.28 – 4.19 (m, 2H), 3.68 (d, *J* = 11.2 Hz, 2H), 3.61 – 3.54 (m, 1H), 3.11 – 2.88 (m, 3H), 2.67 – 2.58 (m, 3H), 2.42 – 2.00 (m, 5H), 1.92 – 1.74 (m, 4H), 1.76 – 1.47 (m, 5H). | C | 794.4 | 794.5 |
| **A79** | $^{1}$H NMR (400 MHz, DMSO) δ 11.19 (s, 1H), 9.35 (s, 1H), 7.96 (d, *J* = 18.4 Hz, 2H), 7.24 – 7.11 (m, 3H), 6.86 – 6.77 (m, 2H), 6.71 (dd, *J* = 15.6, 8.4 Hz, 3H), 6.45 (d, *J* = 8.4 Hz, 2H), 6.39 – 6.30 (m, 2H), 5.22 (dd, *J* = 12.8, 5.2 Hz, 1H), 5.12 (s, 2H), 4.83 (s, 2H), 4.39 (t, *J* = 11.2 Hz, 1H), 4.30 – 4.19 (m, 2H), 3.68 (d, *J* = 11.2 Hz, 2H), 3.59 – 3.56 (m, 1H), 3.12 – 2.90 (m, 3H), 2.73 – 2.61 (m, 3H), 2.43 – 2.27 (m, 2H), 2.20 – 2.01 (m, 3H), 1.93 – 1.77 (m, 4H), 1.73 – 1.52 (m, 5H). | C | 794.4 | 794.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| **A80** | $^1$H NMR (400 MHz, DMSO) δ 11.05 (s, 1H), 9.35 (s, 1H), 7.75 (d, *J* = 13.8 Hz, 1H), 7.62 (d, *J* = 12.6 Hz, 1H), 7.24 – 7.16 (m, 3H), 6.85 – 6.79 (m, 2H), 6.70 (dd, *J* = 16.4, 8.4 Hz, 3H), 6.44 (d, *J* = 8.6 Hz, 2H), 6.39 – 6.31 (m, 2H), 5.17 (dd, *J* = 13.2, 5.2 Hz, 1H), 5.06 (d, *J* = 6.2 Hz, 2H), 4.77 (d, *J* = 7.8 Hz, 2H), 4.52 (d, *J* = 17.2 Hz, 1H), 4.44 – 4.34 (m, 2H), 4.29 – 4.18 (m, 2H), 3.71 – 3.60 (m, 3H), 3.10 – 2.96 (m, 3H), 2.74 – 2.63 (m, 2H), 2.46 – 2.29 (m, 3H), 2.11 – 2.02 (m, 2H), 1.90 – 1.52 (m, 10H). | C | 780.4 | 780.4 |
| **A81** | $^1$H NMR (400 MHz, DMSO) δ 11.05 (s, 1H), 9.34 (s, 1H), 7.75 (d, *J* = 13.8 Hz, 1H), 7.62 (d, *J* = 12.8 Hz, 1H), 7.28 – 7.17 (m, 3H), 6.86 – 6.78 (m, 2H), 6.71 (dd, *J* = 14.8, 8.4 Hz, 3H), 6.45 (d, *J* = 8.4 Hz, 2H), 6.40 – 6.30 (m, 2H), 5.17 (dd, *J* = 13.2, 5.2 Hz, 1H), 5.06 (d, *J* = 4.8 Hz, 2H), 4.77 (d, *J* = 8.0 Hz, 2H), 4.52 (d, *J* = 17.4 Hz, 1H), 4.44 – 4.33 (m, 2H), 4.29 – 4.20 (m, 2H), 3.73 – 3.58 (m, 3H), 3.14 – 2.91 (m, 3H), 2.73 – 2.62 (m, 3H), 2.48 – 2.31 (m, 3H), 2.12 – 2.01 (m, 2H), 1.92 – 1.82 (m, 4H), 1.76 – 1.67 (m, 2H), 1.63 – 1.53 (m, 3H). | C | 780.4 | 780.4 |
| **A82** | DMSO-d6:δ 10.25 (s, 1H), 8.29 (s, 1H), 7.20 – 7.08 (m, 5H), 6.92 (d, J = 8.4 Hz, 2H), 6.81 – 6.73 (m, 2H), 6.63 (dd, 3H), 6.42 – 6.24 (m, 4H), 4.33 (d, J = 11.2 Hz, 1H), 4.24 – 4.13 (m, 2H), 3.69 (t, J = 6.4 Hz, 2H), 3.60 – 3.38 (m, 8H), 3.15 – 2.94 (m, 5H), 2.68 (d, J = 6.0 Hz, 2H), 2.19 (d, J = 6.8 Hz, 2H), 1.83 – 1.57 (m, 3H), 1.24 – 1.08 (m, 2H). | E | 672.3 | 672.3 |
| **A83** | 1H NMR (400 MHz, DMSO) δ 10.25 (s, 1H), 8.24 (s, 1H), 7.18 – 7.07 (m, 5H), 6.91 (d, J = 9.0 Hz, 2H), 6.80 – 6.71 (m, 2H), 6.68 – 6.55 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.24 | E | 712.4 | 712.4 |

| Compound No | $^1$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| | (m, 2H), 4.32 (t, J = 11.0 Hz, 1H), 4.22 – 4.12 (m, 2H), 3.69 (t, J = 6.6 Hz, 2H), 3.53 – 3.48 (m, 1H), 3.13 – 3.04 (m, 4H), 3.01 – 2.94 (m, 2H), 2.92 – 2.85 (m, 2H), 2.67 (t, J = 6.6 Hz, 2H), 2.48 – 2.45 (m, 5H), 2.39 (d, J = 6.8 Hz, 2H), 1.92 (t, J = 9.8 Hz, 2H), 1.67 – 1.58 (m, 2H), 1.53 – 1.47 (m, 2H), 1.41 (t, J = 9.8 Hz, 2H). | | | |
| **A84** | DMSO-d6:δ 10.94 (s, 1H), 9.24 (s, 1H), 7.28 – 6.95 (m, 5H), 6.72 – 6.65 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.53 – 6.44 (m, 1H), 6.35 (d, J = 9.0 Hz, 1H), 6.31 – 6.23 (m, 2H), 6.18 (s, 1H), 5.03 (dd, 1H), 4.62 (d, J = 5.4 Hz, 1H), 4.42 – 4.22 (m, 3H), 4.16 – 3.94 (m, 3H), 3.92 – 3.78 (m, 1H), 3.69 – 3.53 (m, 2H), 3.51 – 3.41 (m, 1H), 3.23 – 3.13 (m, 1H), 3.01 (s, 3H), 2.98 – 2.84 (m, 3H), 2.81 – 2.56 (m, 4H), 2.45 – 2.07 (m, 4H), 2.01 – 1.60 (m, 5H), 1.36 – 1.10 (m, 2H). | E | 784.4 | 784.4 |
| **A85** | 1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.72 (d, J = 8.2 Hz, 1H), 8.37 – 8.14 (m, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.48 – 7.32 (m, 1H), 7.22 – 7.05 (m, 3H), 6.82 – 6.54 (m, 5H), 6.44 – 6.19 (m, 4H), 4.79 – 4.68 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.23 – 4.12 (m, 2H), 3.54 – 3.47 (m, 2H), 3.31 (s, 4H), 3.03 – 2.85 (m, 4H), 2.84 – 2.75 (m, 1H), 2.48 – 2.37 (m, 7H), 2.24 – 2.12 (m, 1H), 2.05 – 1.84 (m, 3H), 1.63 (s, 2H), 1.54 – 1.38 (m, 4H). | F | 755.4 | 755.4 |
| **A86** | DMSO-d6:δ 10.96 (s, 1H), 8.30 (s, 1H), 7.46 (s, 1H), 7.21 – 7.10 (m, 3H), 7.00 (s, 1H), 6.83 – 6.73 (m, 2H), 6.63 (dd, 3H), 6.38 (d, J = 8.4 Hz, 2H), 6.33 – 6.22 (m, 2H), 5.07 (dd, 1H), 4.46 (s, 2H), 4.37 – 4.29 (m, 2H), 4.24 – 4.10 (m, 3H), 3.59 – 3.50 (m, 3H), 2.98 – 2.76 (m, 3H), 2.69 – 2.55 (m, 2H), 2.39 – 2.32 (m, | E | 753.4 | 753.4 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. (M+H)$^{+}$ | Found. (M+H)$^{+}$ |
|---|---|---|---|---|
| | 2H), 2.22 – 2.14 (m, 2H), 2.00 – 1.86 (m, 5H), 1.79 – 1.63 (m, 5H), 1.22 – 1.09 (m, 2H). | | | |
| **A87** | 1H NMR (400 MHz, DMSO) δ 10.25 (s, 1H), 9.28 (s, 1H), 7.14 (s, 5H), 6.94 (s, 2H), 6.82 – 6.53 (m, 5H), 6.39 (s, 2H), 6.34 – 6.21 (m, 2H), 4.25 (d, J = 54.9 Hz, 3H), 3.93 (dd, J = 35.0, 15.7 Hz, 4H), 3.68 (s, 4H), 3.51 (d, J = 14.2 Hz, 1H), 3.14 (d, J = 9.8 Hz, 2H), 2.98 (d, J = 13.9 Hz, 4H), 2.66 (d, J = 14.6 Hz, 4H), 1.79 (dd, J = 43.0, 8.6 Hz, 6H), 1.39 – 1.13 (m, 3H). | C | 812.4 | 812.5 |
| **A88** | DMSO-d6:δ 10.84 (s, 1H), 9.27 (s, 1H), 8.73 (d, J = 8.2 Hz, 1H), 8.32 (s, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.50 – 7.34 (m, 1H), 7.20 – 7.05 (m, 3H), 6.85 – 6.71 (m, 2H), 6.69 – 6.56 (m, 3H), 6.38 (d, J = 8.4 Hz, 2H), 6.32 – 6.22 (m, 2H), 4.82 – 4.69 (m, 1H), 4.33 (t, J = 11.0 Hz, 1H), 4.24 – 4.12 (m, 2H), 3.61 – 3.48 (m, 3H), 3.32 – 3.05 (m, 8H), 2.86 – 2.73 (m, 1H), 2.69 – 2.54 (m, 3H), 2.35 – 2.11 (m, 3H), 2.05 – 1.96 (m, 1H), 1.84 – 1.60 (m, 3H), 1.26 – 1.10 (m, 2H). | E | 715.4 | 715.4 |
| **A89** | 1H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.23 (s, 1H), 7.24 – 7.08 (m, 4H), 7.00 (d, J = 8.4 Hz, 1H), 6.80 – 6.72 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 8.6 Hz, 2H), 6.37 (d, J = 8.6 Hz, 2H), 6.33 – 6.23 (m, 2H), 5.09 – 4.90 (m, 1H), 4.36 – 4.08 (m, 6H), 4.01 – 3.90 (m, 1H), 3.80 (d, J = 11.4 Hz, 1H), 3.52 – 3.47 (m, 1H), 3.18 – 3.12 (m, 1H), 3.01 – 2.94 (m, 2H), 2.92 – 2.82 (m, 5H), 2.77 – 2.67 (m, 1H), 2.61 – 2.53 (m, 2H), 2.43 – 2.37 (m, 3H), 2.10 (t, J = 10.2 Hz, 1H), 2.00 – 1.88 (m, 3H), 1.73 (t, J = 10.6 Hz, 1H), 1.67 – 1.58 (m, 2H), 1.56 – 1.36 (m, 4H). | A | 794.4 | 794.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| **A90** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.25 (s, 1H), 7.21 – 7.08 (m, 4H), 7.00 (d, J = 8.2 Hz, 1H), 6.75 (s, 2H), 6.69 – 6.54 (m, 3H), 6.43 – 6.21 (m, 4H), 5.08 – 4.98 (m, 1H), 4.36 – 4.09 (m, 6H), 4.02 – 3.93 (m, 1H), 3.81 (d, J = 11.4 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.16 – 3.11 (m, 1H), 2.98 (s, 2H), 2.93 – 2.83 (m, 5H), 2.70 (t, J=11.6 Hz,1H), 2.62 – 2.54 (m, 2H), 2.43 – 2.34 (m, 3H), 2.12 (t, J = 10.4 Hz, 1H), 2.00 – 1.85 (m, 3H), 1.74(t, J=10.4 Hz,1H), 1.63 (s, 2H), 1.50 (s, 2H), 1.41(t,J=8.6 Hz, 2H). | A | 794.4 | 794.5 |
| **A91** | DMSO-d6:δ 10.82 (s, 1H), 7.18 – 7.08 (m, 4H), 6.83 – 6.46 (m, 7H), 6.39 – 6.17 (m, 5H), 4.47 – 4.19 (m, 7H), 3.67 – 3.46 (m, 8H), 3.08 (s, 5H), 2.86 – 2.56 (m, 2H), 2.20 – 1.75 (m, 8H). | B | 750.3 | 750.3 |
| **A92** | 1H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 8.30 (s, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.28 – 7.13 (m, 4H), 7.04 (d, J = 7.8 Hz, 2H), 6.90 – 6.78 (m, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.52 (d, J = 8.8 Hz, 1H), 6.36 – 6.25 (m, 2H), 5.13 – 4.96 (m, 1H), 4.33 – 4.14 (m, 5H), 3.36 – 3.21 (m, 10H), 2.96 – 2.85 (m, 1H), 2.65 – 2.56 (m, 1H), 2.50 – 2.34 (m, 8H), 2.02 – 1.87 (m, 3H), 1.59 – 1.48 (m, 2H), 1.46 – 1.36 (m, 4H). | C | 767.4 | 767.4 |
| **A93** | 1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 8.27 (s, 1H), 7.63 – 7.46 (m, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.19 – 7.07 (m, 3H), 6.81 – 6.69 (m, 2H), 6.69 – 6.54 (m, 3H), 6.41 – 6.22 (m, 4H), 4.77 – 4.64 (m, 1H), 4.47 – 4.38 (m, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.22 – 4.13 (m, 2H), 4.09 – 3.99 (m, 1H), 3.78 – 3.73 (m, 1H), 3.50 – 3.48 (m, 2H), 3.22 – 3.13 (m, 2H), 3.01 – 2.95 (m, 2H), 2.93 – 2.86 (m, 4H), 2.79 – 2.69 (m, | B | 783.4 | 783.4 |

| Compound No | $^1$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| | 2H), 2.43 – 2.36 (m, 2H), 2.19 – 2.04 (m, 2H), 2.01 – 1.88 (m, 3H), 1.71 (t, J = 10.8 Hz, 1H), 1.65 – 1.48 (m, 4H), 1.46 – 1.35 (m, 2H). | | | |
| **A94** | 1H NMR (400 MHz, DMSO) δ 10.73 (s, 1H), 8.18 (s, 1H), 7.23 – 7.04 (m, 3H), 6.81 – 6.70 (m, 2H), 6.68 – 6.54 (m, 4H), 6.36 (d, J = 8.8 Hz, 2H), 6.31 – 6.24 (m, 2H), 6.21 – 6.09 (m, 2H), 5.32 – 5.20 (m, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.20 – 4.08 (m, 4H), 3.81 (d, J = 9.6 Hz, 1H), 3.55 – 3.46 (m, 3H), 3.01 – 2.95 (m, 2H), 2.92 – 2.65 (m, 7H), 2.60 – 2.52 (m, 1H), 2.43 – 2.33 (m, 2H), 2.14 – 2.02 (m, 2H), 1.95 – 1.87 (m, 2H), 1.86 – 1.74 (m, 1H), 1.68 (t, J = 10.8 Hz, 1H), 1.64 – 1.46 (m, 4H), 1.44 – 1.35 (m, 2H). | B | 754.4 | 754.4 |
| **A95** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.27 (s, 1H), 7.19 – 7.08 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.69 – 6.53 (m, 5H), 6.40 – 6.21 (m, 4H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.40 – 4.05 (m, 7H), 3.91 – 3.84 (m, 1H), 3.78 (d, J = 11.6 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.13 (d, J = 9.6 Hz, 1H), 3.01 – 2.94 (m, 2H), 2.92 – 2.80 (m, 5H), 2.78 – 2.67 (m, 1H), 2.63 – 2.54 (m, 1H), 2.43 – 2.29 (m, 3H), 2.09 (d, J = 10.4 Hz, 1H), 2.00 – 1.83 (m, 3H), 1.71 (d, J = 10.8 Hz, 1H), 1.65 – 1.47 (m, 4H), 1.45 – 1.33 (m, 2H). | B | 794.4 | 794.5 |
| **A96** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.19 (s, 1H), 7.21 – 7.08 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.80 – 6.68 (m, 2H), 6.67 – 6.49 (m, 3H), 6.44 – 6.21 (m, 4H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.42 – 4.22 (m, 3H), 4.20 – 4.06 (m, 3H), 3.98 – 3.72 (m, 3H), 3.53 – 3.46 (m, 2H), 3.17 – 3.10 (m, 1H), 3.03 – 2.95 (m, 2H), 2.93 – 2.80 (m, 5H), 2.77 – 2.65 (m, 1H), 2.62 – 2.54 (m, 1H), 2.44 – 2.30 | B | 794.4 | 794.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. (M+H)$^{+}$ | Found. (M+H)$^{+}$ |
|---|---|---|---|---|
| | (m, 3H), 2.10 (d, J = 10.4 Hz, 1H), 2.00 – 1.87 (m, 3H), 1.72 (t, J = 10.8 Hz, 1H), 1.65 – 1.46 (m, 4H), 1.44 – 1.35 (m, 2H). | | | |
| **A97** | 1H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 8.61 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.18 – 7.10 (m, 3H), 6.82 – 6.70 (m, 2H), 6.68 – 6.56 (m, 3H), 6.41 – 6.21 (m, 4H), 4.79 – 4.66 (m, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.21 – 4.12 (m, 2H), 4.00 (s, 3H), 3.58 – 3.41 (m, 3H), 3.12 – 2.85 (m, 9H), 2.83 – 2.73 (m, 1H), 2.53 (s, 3H), 2.42 – 2.36 (m, 2H), 2.27 – 2.13 (m, 1H), 2.04 – 1.86 (m, 3H), 1.66 – 1.47 (m, 4H), 1.46 – 1.37 (m, 2H). | C | 785.4 | 785.4 |
| **A98** | 1H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 9.35 (s, 1H), 8.15 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.21 – 7.10 (m, 3H), 7.05 (d, J = 7.8 Hz, 2H), 6.91 – 6.79 (m, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.52 (d, J = 8.8 Hz, 1H), 6.41 – 6.25 (m, 2H), 5.10 – 4.99 (m, 1H), 4.40 – 4.16 (m, 6H), 3.58 – 3.54 (m, 2H), 3.39 – 3.32 (m, 3H), 3.31 – 3.20 (m, 7H), 2.93 – 2.84 (m, 1H), 2.64 – 2.54 (m, 2H), 2.47 – 2.29 (m, 3H), 2.01 – 1.89 (m, 3H), 1.61 – 1.50 (m, 2H), 1.49 – 1.33 (m, 4H). | C | 767.4 | 767.4 |
| **A99** | 1H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 7.45 (s, 1H), 7.24 – 7.07 (m, 3H), 7.00 (s, 1H), 6.82 – 6.72 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.39 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.07 (dd, J = 13.2, 5.2 Hz, 1H), 4.49 – 4.40 (m, 2H), 4.37 – 4.27 (m, 2H), 4.25 – 4.11 (m, 3H), 3.54 – 3.46 (m, 2H), 3.42 – 3.39 (m, 2H), 3.37 – 3.33 (m, 2H), 2.95 – 2.78 (m, 3H), 2.62 – 2.55 (m, 1H), 2.41 – 2.30 (m, 1H), 2.12 (d, J = 6.8 Hz, 2H), 2.02 – 1.79 (m, 7H), 1.73 – 1.60 (m, 4H), | C | 793.4 | 793.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^{+}$ | Found. $(M+H)^{+}$ |
|---|---|---|---|---|
| | 1.55 – 1.37 (m, 3H), 0.98 – 0.83 (m, 2H). | | | |
| **A100** | 1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.38 – 8.22 (m, 1H), 7.92 – 7.76 (m, 1H), 7.47 – 7.28 (m, 1H), 7.21 – 7.10 (m, 3H), 6.85 – 6.58 (m, 4H), 6.35 – 6.23 (m, 3H), 6.15 (d, J = 13.2 Hz, 1H), 4.81 – 4.69 (m, 1H), 4.40 – 4.08 (m, 3H), 3.61 – 3.48 (m, 2H), 3.41 – 3.14 (m, 9H), 2.97 – 2.64 (m, 2H), 2.60 – 2.53 (m, 2H), 2.38 – 1.90 (m, 5H), 1.81 – 1.59 (m, 3H), 1.34 – 1.08 (m, 2H). | C | 733.3 | 733.3 |
| **A101** | 1H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 9.02 (d, J = 8.4 Hz, 1H), 8.58 (s, 1H), 8.22 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.96 – 7.84 (m, 1H), 7.23 – 7.12 (m, 3H), 6.81 – 6.64 (m, 4H), 6.38 – 6.24 (m, 3H), 6.23 – 6.10 (m, 1H), 4.86 – 4.72 (m, 1H), 4.41 – 4.17 (m, 4H), 3.58 – 3.53 (m, 2H), 3.22 (d, J = 8.4 Hz, 2H), 3.02 – 2.94 (m, 2H), 2.86 – 2.75 (m, 1H), 2.73 – 2.62 (m, 1H), 2.22 (d, J = 7.2 Hz, 3H), 2.07 – 1.96 (m, 3H), 1.81 – 1.69 (m, 6H), 1.66 – 1.58 (m, 1H), 1.30 – 1.17 (m, 2H). | C | 732.2 | 732.3 |
| **A102** | 1H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 9.47 – 9.11 (m, 1H), 8.61 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.21 – 7.13 (m, 3H), 6.87 – 6.61 (m, 4H), 6.35 – 6.23 (m, 3H), 6.19 – 6.08 (m, 1H), 4.80 – 4.65 (m, 1H), 4.37 – 4.15 (m, 3H), 4.01 (s, 3H), 3.62 – 3.51 (m, 1H), 3.45 – 3.28 (m, 4H), 3.25 – 3.14 (m, 3H), 3.10 (s, 4H), 2.89 – 2.71 (m, 1H), 2.61 – 2.54 (m, 2H), 2.26 – 2.14 (m, 3H), 2.07 – 1.95 (m, 1H), 1.76 (d, J = 11.8 Hz, 2H), 1.67 – 1.57 (m, 1H), 1.31 – 1.10 (m, 2H). | C | 763.4 | 763.4 |
| **A103** | 1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 7.62 | C | 761.3 | 761.3 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | – 7.51 (m, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.23 – 7.06 (m, 3H), 6.83 – 6.64 (m, 4H), 6.38 – 6.25 (m, 3H), 6.15 (d, J = 13.2 Hz, 1H), 4.76 – 4.66 (m, 1H), 4.48 – 4.40 (m, 1H), 4.36 – 4.17 (m, 3H), 4.12 – 4.03 (m, 1H), 3.78 (d, J = 11.2 Hz, 1H), 3.58 – 3.51 (m, 2H), 3.31 – 3.07 (m, 5H), 2.99 – 2.92 (m, 2H), 2.82 – 2.70 (m, 2H), 2.39 – 1.85 (m, 6H), 1.84 – 1.58 (m, 4H), 1.33 – 1.14 (m, 2H). | | | |
| **A104** | 1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.17 (s, 3H), 6.86 – 6.63 (m, 4H), 6.32 (d, J = 5.8 Hz, 3H), 6.23 – 6.08 (m, 1H), 4.79 – 4.63 (m, 1H), 4.51 – 4.41 (m, 1H), 4.40 – 4.18 (m, 3H), 4.14 – 4.02 (m, 1H), 3.85 – 3.73 (m, 1H), 3.60 – 3.50 (m, 4H), 3.27 – 3.14 (m, 4H), 2.95 (d, J = 9.8 Hz, 2H), 2.88 – 2.73 (m, 2H), 2.29 – 2.08 (m, 4H), 2.03 – 1.93 (m, 1H), 1.87 – 1.61 (m, 4H), 1.30 – 1.17 (m, 2H). | C | 761.3 | 761.3 |
| **A105** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.27 – 6.96 (m, 5H), 6.78 – 6.53 (m, 3H), 6.41 – 6.19 (m, 4H), 5.07 – 4.97 (m, 1H), 4.66 (d, J = 4.4 Hz, 1H), 4.42 – 4.20 (m, 3H), 4.16 – 4.05 (m, 2H), 3.97 (d, J = 9.6 Hz, 1H), 3.83 (d, J = 11.2 Hz, 1H), 3.53 – 3.44 (m, 2H), 3.22 – 3.12 (m, 2H), 3.06 (s, 3H), 3.00 – 2.85 (m, 3H), 2.80 – 2.72 (m, 1H), 2.70 – 2.53 (m, 3H), 2.43 – 2.33 (m, 1H), 2.28 – 2.17 (m, 2H), 2.15 – 2.06 (m, 1H), 2.01 – 1.89 (m, 1H), 1.87 – 1.58 (m, 4H), 1.37 – 1.16 (m, 2H). | C | 802.4 | 802.5 |
| **A106** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.32 (s, 1H), 7.22 – 6.96 (m, 5H), 6.77 – 6.55 (m, 3H), 6.36 – 6.20 (m, 4H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.66 (d, J = 5.6 Hz, 1H), 4.38 – 4.20 (m, 3H), 4.14 – 4.04 (m, 2H), | C | 802.4 | 802.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 4.03 – 3.91 (m, 1H), 3.83 (d, J = 11.2 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.29 – 3.22 (m, 2H), 3.21 – 3.14 (m, 1H), 3.06 (s, 3H), 2.97 – 2.85 (m, 3H), 2.80 – 2.68 (m, 1H), 2.66 – 2.52 (m, 3H), 2.43 – 2.32 (m, 1H), 2.27 – 2.18 (m, 2H), 2.14 – 2.04 (m, 1H), 2.01 – 1.90 (m, 1H), 1.85 – 1.59 (m, 4H), 1.36 – 1.17 (m, 2H). | | | |
| **A107** | $^{1}$H NMR (400 MHz, DMSO) δ 10.24 (s, 1H), 8.33 (s, 2H), 7.25 – 7.06 (m, 5H), 6.91 (d, *J* = 9.2 Hz, 2H), 6.80 – 6.73 (m, 2H), 6.63 (dd, *J* = 22.6, 8.4 Hz, 3H), 6.39 (d, *J* = 8.6 Hz, 2H), 6.33 – 6.23 (m, 2H), 4.33 (t, *J* = 11.2 Hz, 1H), 4.24 – 4.15 (m, 2H), 3.69 (t, *J* = 6.6 Hz, 3H), 3.16 – 3.08 (m, 3H), 3.07 – 2.94 (m, 7H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.45 – 2.40 (m, 4H), 1.94 (t, *J* = 9.8 Hz, 2H), 1.72 – 1.64 (m, 2H), 1.60 – 1.52 (m, 2H), 1.50 – 1.39 (m, 2H). | B | 712.4 | 712.4 |
| **A108** | DMSO-d6:δ 10.88 (s, 1H), 9.26 (s, 1H), 8.62 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.0 Hz, 1H), 7.19 – 7.10 (m, 3H), 6.81 – 6.72 (m, 2H), 6.64 (d, J = 8.2 Hz, 1H), 6.41 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 4.79 – 4.67 (m, 1H), 4.32 (d, J = 11.0 Hz, 1H), 4.22 – 4.12 (m, 2H), 4.01 (s, 3H), 3.54 – 3.35 (m, 6H), 3.10 (s, 4H), 2.89 – 2.75 (m, 1H), 2.66 – 2.54 (m, 2H), 2.44 – 1.94 (m, 6H), 1.84 (d, J = 12.0 Hz, 2H), 1.69 (d, J = 11.4 Hz, 2H), 1.51 – 1.38 (m, 2H), 1.04 – 0.84 (m, 2H). | E | 785.4 | 785.5 |
| **A109** | 1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 9.32 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 2.8 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.41 (dd, J = 8.8, 2.8 Hz, 1H), 7.20 – 6.98 (m, 3H), 6.79 – 6.55 (m, 3H), 6.35 – 6.16 (m, 4H), 4.79 – 4.62 (m, 2H), 4.32 (d, J = 11.2 Hz, 1H), 4.13 – 4.04 (m, 1H), | B | 763.4 | 763.4 |

| Compound No | ¹HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 3.52 – 3.44 (m, 1H), 3.36 – 3.26 (m, 11H), 3.06 (s, 3H), 2.84 – 2.73 (m, 1H), 2.69 – 2.54 (m, 2H), 2.27 – 2.12 (m, 3H), 2.05 – 1.93 (m, 1H), 1.85 – 1.57 (m, 3H), 1.35 – 1.13 (m, 2H). | | | |
| **A110** | 1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.32 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.12 (s, 3H), 6.80 – 6.53 (m, 3H), 6.41 – 6.18 (m, 4H), 4.81 – 4.62 (m, 2H), 4.32 (d, J = 11.2 Hz, 1H), 4.09 (d, J = 8.4 Hz, 1H), 3.56 – 3.44 (m, 2H), 3.40 – 3.21 (m, 11H), 3.06 (s, 3H), 2.84 – 2.72 (m, 1H), 2.68 – 2.57 (m, 2H), 2.28 – 2.11 (m, 3H), 2.05 – 1.96 (m, 1H), 1.87 – 1.59 (m, 3H), 1.32 – 1.16 (m, 2H). | B | 763.4 | 763.4 |
| **A111** | 1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 9.27 (s, 1H), 8.68 (d, J = 8.1 Hz, 1H), 8.29 (d, J = 2.7 Hz, 1H), 8.16 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.17 – 7.10 (m, 3H), 6.76 (d, J = 3.8 Hz, 2H), 6.63 (dd, J = 17.4, 8.5 Hz, 3H), 6.37 (d, J = 8.5 Hz, 2H), 6.32 – 6.24 (m, 2H), 4.78 – 4.67 (m, 1H), 4.32 (t, J = 11.3 Hz, 1H), 4.18 (t, J = 5.9 Hz, 2H), 3.91 (d, J = 12.4 Hz, 2H), 3.51 (dd, J = 14.6, 5.0 Hz, 1H), 3.11 (s, 4H), 2.96 (s, 4H), 2.80 (dd, J = 24.4, 12.5 Hz, 3H), 2.67 (s, 1H), 2.33 (s, 2H), 2.24 – 2.10 (m, 1H), 2.05 – 1.94 (m, 1H), 1.75 (d, J = 14.9 Hz, 6H), 1.55 (dd, J = 18.2, 9.2 Hz, 1H), 1.19 (dd, J = 23.8, 12.8 Hz, 2H). | B | 755.4 | 755.5 |
| **A112** | ¹H NMR (400 MHz, DMSO) δ 10.24 (s, 1H), 8.27 (s, 1H), 7.22 – 7.03 (m, 5H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.83 – 6.71 (m, 2H), 6.62 (dd, *J* = 22.6, 8.4 Hz, 3H), 6.38 (d, *J* = 8.4 Hz, 2H), 6.35 – 6.18 (m, 2H), 4.31 (t, *J* = 11.2 Hz, 1H), 4.24 – 4.13 (m, 2H), 3.68 (t, *J* = 6.6 Hz, 2H), 3.56 – 3.46 (m, 2H), 3.14 – 3.06 (m, 2H), 3.04 – 2.94 (m, | C | 712.4 | 712.4 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 6H), 2.67 (t, *J* = 6.6 Hz, 2H), 2.44 – 2.36 (m, 6H), 1.97 – 1.89 (m, 2H), 1.71 – 1.62 (m, 2H), 1.59 – 1.51 (m, 2H), 1.47 – 1.39 (m, 2H). | | | |
| **A113** | DMSO-d6:δ 10.97 (s, 1H), 9.49 – 9.02 (m, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.21 – 7.07 (m, 3H), 6.79 – 6.71 (m, 2H), 6.63 (dd, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.31 – 6.24 (m, 2H), 5.08 (dd, 1H), 4.51 (s, 2H), 4.42 – 4.28 (m, 2H), 4.25 – 4.11 (m, 3H), 3.52 – 3.48 (m, 1H), 3.02 – 2.85 (m, 5H), 2.83 – 2.76 (m, 2H), 2.70 – 2.53 (m, 2H), 2.43 – 2.31 (m, 3H), 2.02 – 1.83 (m, 7H), 1.70 – 1.59 (m, 4H), 1.54 – 1.47 (m, 2H), 1.45 – 1.35 (m, 2H). | E | 792.4 | 794.5 |
| **A114** | DMSO-d6:δ 10.97 (s, 1H), 9.27 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.19 – 7.09 (m, 3H), 6.80 – 6.72 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.42 – 6.23 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.08 (dd, 1H), 4.51 (s, 2H), 4.41 – 4.28 (m, 2H), 4.25 – 4.11 (m, 3H), 3.54 – 3.37 (m, 5H), 2.97 – 2.77 (m, 3H), 2.68 – 2.55 (m, 1H), 2.43 – 2.30 (m, 1H), 2.12 (d, J = 6.8 Hz, 2H), 2.01 – 1.81 (m, 7H), 1.75 – 1.62 (m, 4H), 1.55 – 1.38 (m, 3H), 0.99 – 0.84 (m, 2H). | E | 792.4 | 794.5 |
| **A115** | DMSO-d6δ 10.93 (s, 1H), 9.26 (s, 1H), 7.23 – 7.10 (m, 4H), 7.07 – 6.97 (m, 1H), 6.81 – 6.71 (m, 2H), 6.64 (d, J = 8.2 Hz, 1H), 6.40 – 6.22 (m, 4H), 6.09 (d, J = 8.2 Hz, 2H), 5.08 – 4.98 (m, 1H), 4.45 – 4.07 (m, 6H), 4.02 – 3.75 (m, 2H), 3.67 – 3.36 (m, 5H), 3.24 – 3.13 (m, 1H), 2.99 – 2.83 (m, 3H), 2.79 – 2.70 (m, 1H), 2.67 – 2.56 (m, 1H), 2.49 – 2.30 (m, 2H), 2.19 – 2.03 (m, 2H), 2.00 – 1.92 (m, 1H), 1.89 – 1.80 (m, 2H), 1.77 – 1.63 (m, 3H), 1.58 – 1.37 (m, 3H), 1.04 – 0.81 (m, 2H). | E | 794.4 | 794.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| **A116** | 1H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 8.85 (d, J = 8.2 Hz, 1H), 8.27 (s, 1H), 8.04 (s, 1H), 7.55 (s, 1H), 7.19 – 7.07 (m, 3H), 6.81 – 6.71 (m, 2H), 6.69 – 6.56 (m, 3H), 6.42 – 6.22 (m, 4H), 4.80 – 4.69 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.22 – 4.13 (m, 2H), 3.93 (s, 3H), 3.53 – 3.47 (m, 2H), 3.10 (s, 4H), 3.01 – 2.86 (m, 4H), 2.85 – 2.74 (m, 1H), 2.59 – 2.52 (m, 2H), 2.48 – 2.37 (m, 5H), 2.24 – 2.13 (m, 1H), 2.05 – 1.86 (m, 3H), 1.62 -1.36 (m, 6H). | E | 784.4 | 784.4 |
| **A117** | 1H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 9.26 (s, 1H), 8.86 (d, J = 8.2 Hz, 1H), 8.05 (s, 1H), 7.57 (s, 1H), 7.14 (s, 3H), 6.76 (s, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.38 – 6.20 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 4.75 (t, J = 12.8 Hz, 1H), 4.31 (d, J = 11.2 Hz, 1H), 4.21 – 4.10 (m, 2H), 3.93 (s, 3H), 3.49 (d, J = 11.2 Hz, 2H), 3.13 (s, 6H), 2.93 – 2.62 (m, 2H), 2.45 – 2.13 (m, 4H), 2.11 – 1.98 (m, 2H), 1.97 – 1.60 (m, 5H), 1.59 – 1.24 (m, 4H), 1.24 (s, 1H), 0.98 – 0.79 (m, 2H). | E | 784.4 | 784.4 |
| **A118** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.27 – 7.10 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.82 – 6.71 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.38 – 6.21 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.37 – 4.09 (m, 6H), 3.92 – 3.77 (m, 2H), 3.51 – 3.47 (m, 1H), 3.41 – 3.32 (m, 5H), 3.18 – 3.12 (m, 1H), 2.96 – 2.84 (m, 3H), 2.80 – 2.71 (m, 1H), 2.62 – 2.54 (m, 1H), 2.39 – 2.30 (m, 1H), 2.17 – 2.03 (m, 3H), 1.98 – 1.91 (m, 1H), 1.87 – 1.76 (m, 2H), 1.75 – 1.62 (m, 3H), 1.54 – 1.38 (m, 3H), 1.00 – 0.80 (m, 2H). | C | 794.4 | 794.5 |
| **A119** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.17 – 7.08 (m, 3H), 7.03 (s, | C | 794.4 | 794.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^{+}$ | Found. $(M+H)^{+}$ |
|---|---|---|---|---|
| | 1H), 6.91 (d, J = 12.4 Hz, 1H), 6.80 – 6.70 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.40 – 6.20 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.38 – 4.11 (m, 6H), 3.92 – 3.76 (m, 2H), 3.52 – 3.47 (m, 1H), 3.41 – 3.33 (m, 5H), 3.19 – 3.13 (m, 1H), 2.96 – 2.83 (m, 3H), 2.80 – 2.71 (m, 1H), 2.61 – 2.53 (m, 1H), 2.37 – 2.27 (m, 1H), 2.18 – 2.02 (m, 3H), 1.99 – 1.89 (m, 1H), 1.87 – 1.78 (m, 2H), 1.73 – 1.61 (m, 3H), 1.54 – 1.36 (m, 3H), 0.98 – 0.82 (m, 2H). | | | |
| **A120** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.19 – 7.05 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.79 – 6.70 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.41 – 6.21 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.38 – 4.23 (m, 3H), 4.21 – 4.07 (m, 3H), 3.93 – 3.78 (m, 2H), 3.51 – 3.47 (m, 1H), 3.43 – 3.30 (m, 5H), 3.18 – 3.12 (m, 1H), 2.94 – 2.83 (m, 3H), 2.78 – 2.71 (m, 1H), 2.61 – 2.54 (m, 1H), 2.38 – 2.28 (m, 1H), 2.18 – 2.02 (m, 3H), 1.98 – 1.90 (m, 1H), 1.88 – 1.77 (m, 2H), 1.75 – 1.62 (m, 3H), 1.55 – 1.33 (m, 3H), 0.98 – 0.80 (m, 2H). | C | 794.4 | 794.5 |
| **A121** | 1H NMR (400 MHz, DMSO) δ 11.18 (s, 1H), 10.94 (s, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.19 – 7.05 (m, 4H), 6.77 – 6.55 (m, 4H), 6.37 – 6.23 (m, 2H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.76 – 4.65 (m, 1H), 4.46 – 4.39 (m, 1H), 4.33 – 4.06 (m, 6H), 3.97 – 3.87 (m, 1H), 3.69 – 3.48 (m, 9H), 3.19 – 3.03 (m, 6H), 2.98 – 2.83 (m, 2H), 2.71 – 2.52 (m, 3H), 2.46 – 2.33 (m, 1H), 2.27 – 1.88 (m, 4H), 1.71 (s, 1H). | C | 784.4 | 784.5 |
| **A122** | 1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.29 – 6.95 (m, 5H), 6.71 – 6.41 (m, 5H), 6.38 – 6.18 (m, 3H), 5.08 – 4.99 (m, 1H), 4.65 (d, J = 5.2 | C | 784.4 | 784.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. (M+H)$^{+}$ | Found. (M+H)$^{+}$ |
|---|---|---|---|---|
| | Hz, 1H), 4.38 – 4.16 (m, 7H), 4.08 – 4.00 (m, 2H), 3.75 – 3.56 (m, 5H), 3.50 – 3.44 (m, 1H), 3.26 – 3.16 (m, 1H), 3.17 – 3.05 (m, 3H), 2.95 – 2.84 (m, 2H), 2.78 – 2.66 (m, 2H), 2.64 – 2.52 (m, 3H), 2.41 – 2.32 (m, 1H), 2.07 – 1.75 (m, 4H), 1.43 – 1.27 (m, 2H). | | | |
| **A123** | 1H NMR (400 MHz, MeOD) δ 8.49 (s, 1H), 7.38 (s, 1H), 7.26 (d, J = 2.4 Hz, 1H), 7.20 – 7.11 (m, 4H), 6.85 – 6.78 (m, 3H), 6.71 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 8.8 Hz, 1H), 6.37 – 6.30 (m, 2H), 5.11 (dd, J = 13.2, 5.2 Hz, 1H), 4.55 (s, 2H), 4.44 – 4.32 (m, 3H), 4.26 – 4.19 (m, 2H), 3.58 – 3.51 (m, 1H), 3.39 – 3.35 (m, 2H), 3.30 – 3.29 (m, 3H), 3.03 – 2.94 (m, 2H), 2.91 – 2.84 (m, 1H), 2.81 – 2.65 (m, 4H), 2.54 – 2.42 (m, 1H), 2.27 – 2.02 (m, 6H), 1.99 – 1.89 (m, 2H), 1.81 – 1.46 (m, 7H). | C | 794.4 | 794.5 |
| **A124** | 1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.71 (d, J = 8.4 Hz, 1H), 8.32 (s, 2H), 7.86 (d, J = 8.8 Hz, 1H), 7.41 (dd, J = 8.8, 2.8 Hz, 1H), 7.17 – 7.03 (m, 3H), 6.73 – 6.63 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.39 – 6.32 (m, 1H), 6.30 – 6.21 (m, 2H), 6.20 – 6.13 (m, 1H), 4.79 – 4.68 (m, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.31 (d, J = 11.2 Hz, 1H), 4.09 – 3.97 (m, 1H), 3.63 – 3.55 (m, 3H), 3.48 – 3.41 (m, 3H), 3.38 – 3.28 (m, 6H), 3.02 (s, 3H), 2.83 – 2.74 (m, 1H), 2.64 – 2.58 (m, 2H), 2.24 – 2.11 (m, 3H), 2.05 – 1.95 (m, 1H), 1.82 – 1.63 (m, 3H), 1.26 – 1.11 (m, 2H). | C | 745.4 | 745.4 |
| **A125** | 1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.32 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.14 – 7.07 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.77 – 6.66 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.34 – 6.19 (m, 4H), 5.06 – 4.99 (m, 1H), | E | 842.4 | 842.5 |

| Compound No | ¹HNMR | LCMS method | Calcd. (M+H)⁺ | Found. (M+H)⁺ |
|---|---|---|---|---|
| | 4.65 (d, J = 5.2 Hz, 1H), 4.39 – 4.21 (m, 3H), 4.16 – 4.05 (m, 2H), 3.95 (t, J = 9.6 Hz, 1H), 3.80 (d, J = 11.6 Hz, 1H), 3.50 – 3.46 (m, 1H), 3.20 – 3.10 (m, 1H), 3.05 (s, 3H), 2.96 – 2.70 (m, 8H), 2.62 – 2.53 (m, 1H), 2.47 – 2.32 (m, 4H), 2.11 (t, J = 10.2 Hz, 1H), 2.01 – 1.89 (m, 3H), 1.79 – 1.63 (m, 3H), 1.62 – 1.52 (m, 2H), 1.44 (t, J = 9.4 Hz, 2H). | | | |
| **A126** | 1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.33 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.13 – 7.07 (m, 3H), 7.00 (d, J = 8.6 Hz, 1H), 6.77 – 6.66 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.35 – 6.19 (m, 4H), 5.07 – 4.99 (m, 1H), 4.65 (d, J = 5.0 Hz, 1H), 4.39 – 4.22 (m, 3H), 4.14 – 4.04 (m, 2H), 3.99 – 3.91 (m, 1H), 3.80 (d, J = 11.8 Hz, 1H), 3.51 – 3.47 (m, 1H), 3.19 – 3.11 (m, 1H), 3.05 (s, 3H), 2.96 – 2.68 (m, 8H), 2.62 – 2.53 (m, 1H), 2.47 – 2.32 (m, 4H), 2.11 (t, J = 10.6 Hz, 1H), 2.02 – 1.89 (m, 3H), 1.79 – 1.38 (m, 7H). | E | 842.4 | 842.5 |
| **A127** | 1H NMR (400 MHz, DMSO) δ 10.86 (s, 1H), 9.51 – 9.12 (m, 2H), 8.86 (d, J = 8.4 Hz, 1H), 8.14 (s, 1H), 7.64 (s, 1H), 7.15 – 7.00 (m, 3H), 6.72 – 6.38 (m, 5H), 6.32 – 6.19 (m, 3H), 4.80 – 4.69 (m, 1H), 4.64 (d, J = 5.6 Hz, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.06 (d, J = 7.2 Hz, 1H), 3.97 (s, 3H), 3.50 – 3.44 (m, 3H), 3.24 – 3.11 (m, 6H), 3.04 (s, 3H), 2.86 – 2.76 (m, 1H), 2.71 – 2.65 (m, 2H), 2.54 – 2.53 (m, 3H), 2.36 – 2.11 (m, 2H), 2.07 – 1.93 (m, 2H), 1.86 – 1.76 (m, 2H), 1.40 – 1.24 (m, 2H). | C | 775.4 | 775.5 |
| **A128** | ¹H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.69 (d, *J* = 8.2 Hz, 1H), 8.38 – 8.17 (m, 2H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.39 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.22 – 7.04 (m, 3H), 6.84 – 6.72 (m, | C | 715.4 | 715.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 2H), 6.63 (dd, *J* = 18.8, 8.4 Hz, 3H), 6.47 – 6.20 (m, 4H), 4.82 – 4.64 (m, 1H), 4.33 (t, *J* = 11.2 Hz, 1H), 4.25 – 4.13 (m, 2H), 3.93 (d, *J* = 12.4 Hz, 2H), 3.61 – 3.44 (m, 1H), 3.01 (s, 4H), 2.91 – 2.73 (m, 3H), 2.47 – 2.39 (m, 5H), 2.25 – 2.10 (m, 3H), 2.06 – 1.95 (m, 1H), 1.80 (d, *J* = 10.6 Hz, 3H), 1.26 – 1.10 (m, 2H). | | | |
| **A129** | $^1$H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.70 (d, *J* = 8.0 Hz, 1H), 8.31 – 8.26 (m, 2H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.43 – 7.36 (m, 1H), 7.20 – 7.11 (m, 3H), 6.83 – 6.72 (m, 2H), 6.64 (dd, *J* = 19.2, 8.4 Hz, 3H), 6.44 – 6.25 (m, 4H), 4.79 – 4.68 (m, 1H), 4.34 (t, *J* = 11.2 Hz, 1H), 4.24 – 4.15 (m, 2H), 3.93 (d, *J* = 12.2 Hz, 2H), 3.01 (s, 5H), 2.90 – 2.75 (m, 4H), 2.45 (s, 4H), 2.19 (d, *J* = 6.0 Hz, 3H), 2.07 – 1.96 (m, 1H), 1.81 (d, *J* = 10.8 Hz, 3H), 1.25 – 1.13 (m, 2H). | B | 715.4 | 715.4 |
| **A130** | 1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.29 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 3.6 Hz, 3H), 6.78 – 6.68 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.35 – 6.21 (m, 4H), 5.12 – 5.04 (m, 1H), 4.65 (d, J = 5.2 Hz, 1H), 4.55 – 4.46 (m, 2H), 4.42 – 4.27 (m, 2H), 4.21 (d, J = 17.0 Hz, 1H), 4.08 (d, J = 7.8 Hz, 1H), 3.50 – 3.48 (m, 1H), 3.05 (s, 3H), 2.94 – 2.75 (m, 7H), 2.59 (d, J = 16.6 Hz, 1H), 2.47 – 2.33 (m, 4H), 2.05 – 1.84 (m, 7H), 1.72 – 1.52 (m, 6H), 1.43 (t, J = 9.4 Hz, 2H). | E | 841.4 | 841.5 |
| **A131** | 1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.19 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.16 – 7.07 (m, 3H), 6.77 – 6.68 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.35 – 6.21 (m, 4H), 5.12 – 5.05 (m, 1H), 4.65 (d, J = 5.4 Hz, 1H), 4.56 – 4.48 | E | 841.4 | 841.6 |

| Compound No | $^1$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| | (m, 2H), 4.41 – 4.27 (m, 2H), 4.21 (d, J = 17.0 Hz, 1H), 4.13 – 4.05 (m, 1H), 3.51 – 3.47 (m, 1H), 3.05 (s, 3H), 2.94 – 2.76 (m, 7H), 2.59 (d, J = 16.0 Hz, 1H), 2.48 – 2.33 (m, 4H), 2.11 – 1.85 (m, 7H), 1.73 – 1.62 (m, 4H), 1.60 – 1.52 (m, 2H), 1.49 – 1.39 (m, 2H). | | | |
| **A132** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.28 (s, 1H), 7.23 – 7.07 (m, 4H), 7.01 (d, J = 8.0 Hz, 1H), 6.80 – 6.70 (m, 2H), 6.69 – 6.55 (m, 3H), 6.37 (d, J = 8.8 Hz, 2H), 6.31 – 6.22 (m, 2H), 5.10 – 4.98 (m, 1H), 4.39 – 4.24 (m, 3H), 4.21 – 4.12 (m, 2H), 4.08 (s, 1H), 4.00 – 3.94 (m, 1H), 3.87 (d, J = 7.8 Hz, 1H), 3.81 (s, 1H), 3.55 – 3.47 (m, 1H), 3.43 (d, J = 7.6 Hz, 1H), 3.33 (s, 4H), 3.06 (s, 3H), 2.88 (d, J = 12.6 Hz, 1H), 2.70 (d, J = 16.0 Hz, 1H), 2.37 – 2.32 (m, 2H), 2.12 (s, 1H), 2.01 – 1.91 (m, 3H), 1.83 – 1.72 (m, 1H), 1.64 – 1.52 (m, 4H), 1.40 – 1.20 (m, 4H). | D | 810.4 | 810.5 |
| **A133** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.22 – 7.10 (m, 4H), 7.01 (d, J = 8.2 Hz, 1H), 6.78 – 6.71 (m, 2H), 6.70 – 6.56 (m, 3H), 6.42 – 6.31 (m, 2H), 6.31 – 6.23 (m, 2H), 5.09 – 5.00 (m, 1H), 4.44 – 4.22 (m, 3H), 4.19 – 4.12 (m, 2H), 4.08 (s, 1H), 3.95 (d, J = 9.4 Hz, 1H), 3.89 – 3.76 (m, 2H), 3.56 – 3.48 (m, 1H), 3.46 – 3.40 (m, 1H), 3.32 (s, 4H), 3.16 (s, 1H), 3.06 (s, 3H), 2.91 (d, J = 12.6 Hz, 1H), 2.73 (s, 1H), 2.38 – 2.34 (m, 2H), 2.13 (d, J = 12.0 Hz, 1H), 2.01 – 1.88 (m, 3H), 1.81 – 1.70 (m, 1H), 1.64 – 1.47 (m, 4H), 1.37 – 1.29 (m, 1H), 1.24 (s, 2H). | E | 810.4 | 810.5 |
| **A134** | 1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.31 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.17 – 7.04 | B | 773.4 | 773.4 |

| Compound No | $^1$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| | (m, 3H), 6.74 – 6.64 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 7.6 Hz, 1H), 6.31 – 6.21 (m, 2H), 6.18 (s, 1H), 4.76 – 4.66 (m, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.51 – 4.38 (m, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.13 – 4.00 (m, 2H), 3.78 (d, J = 11.6 Hz, 1H), 3.65 – 3.56 (m, 2H), 3.49 – 3.39 (m, 2H), 3.23 – 3.17 (m, 1H), 3.05 – 2.92 (m, 5H), 2.84 – 2.70 (m, 2H), 2.63 – 2.55 (m, 2H), 2.25 – 1.94 (m, 5H), 1.84 – 1.62 (m, 4H), 1.25 – 1.11 (m, 2H). | | | |
| **A135** | 1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.27 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.16 – 7.02 (m, 3H), 6.72 – 6.64 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 8.4 Hz, 1H), 6.30 – 6.21 (m, 2H), 6.21 – 6.13 (m, 1H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.57 – 4.48 (m, 2H), 4.40 – 4.16 (m, 3H), 4.08 – 4.00 (m, 1H), 3.63 – 3.55 (m, 2H), 3.48 – 3.42 (m, 2H), 3.02 (s, 3H), 2.92 – 2.76 (m, 2H), 2.68 – 2.55 (m, 3H), 2.44 – 2.30 (m, 1H), 2.19 (d, J = 6.8 Hz, 2H), 2.03 – 1.85 (m, 5H), 1.82 – 1.59 (m, 5H), 1.26 – 1.12 (m, 2H). | B | 783.4 | 783.4 |
| **A136** | 1H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 9.23 (s, 1H), 7.46 (s, 1H), 7.16 – 7.02 (m, 3H), 7.00 (s, 1H), 6.72 – 6.64 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.39 – 6.31 (m, 1H), 6.30 – 6.22 (m, 2H), 6.17 (s, 1H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.49 – 4.43 (m, 2H), 4.37 – 4.16 (m, 3H), 4.09 – 4.00 (m, 1H), 3.63 – 3.54 (m, 2H), 3.48 – 3.41 (m, 2H), 3.02 (s, 3H), 2.94 – 2.79 (m, 2H), 2.63 – 2.54 (m, 3H), 2.41 – 2.31 (m, 1H), 2.19 (d, J = 6.8 Hz, 2H), 2.02 – 1.84 (m, 5H), | B | 783.4 | 783.4 |

| Compound No | $^1$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| | 1.81 – 1.60 (m, 5H), 1.26 – 1.11 (m, 2H). | | | |
| **A137** | 1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.27 (s, 1H), 8.14 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.16 – 7.08 (m, 3H), 6.80 – 6.72 (m, 2H), 6.69 – 6.56 (m, 3H), 6.38 (d, J = 8.8 Hz, 2H), 6.34 – 6.24 (m, 2H), 5.08 (dd, 5.0 Hz, 1H), 4.56 – 4.49 (m, 2H), 4.40 – 4.24 (m, 2H), 4.23 – 4.13 (m, 3H), 3.87 (t, J = 7.8 Hz, 1H), 3.55 – 3.41 (m, 3H), 3.06 (s, 4H), 2.98 – 2.61 (m, 4H), 2.56 (s, 1H), 2.34 (d, J = 7.0 Hz, 2H), 1.99 – 1.90 (m, 4H), 1.71 – 1.55 (m, 6H), 1.39 – 1.28 (m, 1H), 1.24 (s, 2H). | A | 809.4 | 809.5 |
| **A138** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.17 – 7.11 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.80 – 6.72 (m, 2H), 6.69 – 6.57 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.21 (m, 2H), 5.05 – 4.98 (m, 1H), 4.71 – 3.89 (m, 7H), 3.88 – 3.67 (m, 2H), 3.51 (d, J = 4.0 Hz, 1H), 3.44 (t, J = 7.8 Hz, 1H), 3.35 (s, 1H), 3.15 (s, 1H), 3.06 (s, 2H), 2.95 – 2.84 (m, 2H), 2.76 (s, 1H), 2.63 – 2.54 (m, 2H), 2.33 (t, J = 8.8 Hz, 3H), 2.17 – 2.07 (m, 1H), 1.98 – 1.88 (m, 2H), 1.76 – 1.68 (m, 1H), 1.66 – 1.33 (m, 5H), 1.24 (s, 2H). | A | 810.4 | 810.5 |
| **A139** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.18 – 7.07 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.78 – 6.71 (m, 2H), 6.69 – 6.60 (m, 3H), 6.37 (d, J = 8.8 Hz, 2H), 6.31 – 6.23 (m, 2H), 5.08 – 4.97 (m, 1H), 4.36 – 4.21 (m, 3H), 4.20 – 4.11 (m, 3H), 3.93 – 3.84 (m, 2H), 3.81 (d, J = 12.6 Hz, 1H), 3.51 (d, J = 11.4 Hz, 1H), 3.43 (d, J = 8.2 Hz, 1H), 3.06 (s, 4H), 2.96 – 2.84 (m, 2H), 2.76 (s, 1H), 2.60 (s, 1H), 2.33 (s, 3H), 2.05 – 1.91 | A | 810.4 | 810.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^{+}$ | Found. $(M+H)^{+}$ |
|---|---|---|---|---|
| | (m, 3H), 1.61 (d, J = 14.0 Hz, 4H), 1.28 (d, J = 18.2 Hz, 3H). | | | |
| **A140** | 1H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 7.21 – 7.06 (m, 3H), 6.94 (d, J = 8.4 Hz, 2H), 6.79 – 6.70 (m, 2H), 6.69 – 6.54 (m, 3H), 6.37 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.63 (d, J = 7.2 Hz, 1H), 4.35 – 4.13 (m, 4H), 3.51 – 3.45 (m, 1H), 3.41 – 3.39 (m, 2H), 3.35 – 3.33 (m, 2H), 2.91 (d, J = 10.8 Hz, 2H), 2.77 – 2.68 (m, 1H), 2.61 – 2.57 (m, 1H), 2.35 – 2.28 (m, 1H), 2.14 – 2.04 (m, 3H), 2.00 – 1.91 (m, 2H), 1.89 – 1.78 (m, 3H), 1.74 – 1.37 (m, 10H), 0.95 – 0.84 (m, 2H). | C | 725.4 | 725.4 |
| **A141** | 1H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 7.22 – 7.03 (m, 3H), 6.94 (d, J = 8.4 Hz, 2H), 6.80 – 6.71 (m, 2H), 6.69 – 6.54 (m, 3H), 6.45 – 6.18 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.64 (d, J = 6.4 Hz, 1H), 4.35 – 4.11 (m, 6H), 3.51 – 3.47 (m, 1H), 3.41 – 3.29 (m, 4H), 3.01 – 2.91 (m, 2H), 2.78 – 2.69 (m, 1H), 2.62 – 2.53 (m, 1H), 2.38 – 2.27 (m, 1H), 2.24 – 2.15 (m, 2H), 2.13 – 1.98 (m, 3H), 1.91 – 1.77 (m, 3H), 1.73 – 1.57 (m, 6H), 1.53 – 1.35 (m, 2H), 0.97 – 0.84 (m, 2H). | C | 725.4 | 725.4 |
| **A142** | 1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.21 – 7.09 (m, 3H), 6.79 – 6.69 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.36 – 6.23 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 4.74 – 4.66 (m, 1H), 4.47 – 4.38 (m, 1H), 4.37 – 4.27 (m, 1H), 4.20 – 4.02 (m, 3H), 3.77 (d, J = 11.2 Hz, 1H), 3.52 – 3.46 (m, 2H), 3.40 – 3.38 (m, 2H), 3.36 – 3.34 (m, 2H), 3.24 – 3.14 (m, 2H), 2.92 (d, J = 10.4 Hz, 2H), 2.81 – 2.71 (m, 2H), 2.21 – 1.96 (m, 5H), 1.83 (d, J = 12.8 Hz, 2H), 1.76 – 1.62 (m, 3H), 1.54 – 1.37 (m, 3H), 0.97 – 0.85 (m, 2H). | C | 783.4 | 783.4 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| **A143** | 1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.27 (s, 1H), 7.59 (dd, J = 7.6, 2.0 Hz, 1H), 7.39 – 7.25 (m, 3H), 7.15 – 7.10 (m, 3H), 6.76 (dd, J = 6.4, 2.8 Hz, 2H), 6.63 (dd, J = 19.6, 8.8 Hz, 3H), 6.37 (d, J = 8.8 Hz, 2H), 6.31 – 6.23 (m, 2H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.57 – 4.50 (m, 2H), 4.39 – 4.29 (m, 2H), 4.23 – 4.14 (m, 3H), 3.53 – 3.48 (m, 1H), 2.99 (s, 3H), 2.90 (s, 3H), 2.58 (d, J = 18.4 Hz, 3H), 2.29 (d, J = 33.2 Hz, 2H), 1.95 (t, J = 9.6 Hz, 6H), 1.74 (d, J = 10.0 Hz, 2H), 1.57 (d, J = 47.2 Hz, 4H), 1.48 – 1.40 (m, 2H). | C | 793.4 | 793.4 |
| **A144** | 1H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 9.27 (s, 1H), 8.86 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.57 (s, 1H), 7.25 – 7.01 (m, 3H), 6.82 – 6.71 (m, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.36 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 4.79 – 4.71 (m, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.21 – 4.10 (m, 2H), 3.93 (s, 3H), 3.52 – 3.46 (m, 1H), 3.41 – 3.38 (m, 2H), 3.36 – 3.33 (m, 3H), 3.12 (s, 4H), 2.84 – 2.74 (m, 1H), 2.51 – 2.50 (m, 4H), 2.25 – 2.09 (m, 3H), 2.04 – 1.94 (m, 1H), 1.83 (d, J = 12.8 Hz, 2H), 1.69 (d, J = 10.8 Hz, 2H), 1.54 – 1.37 (m, 3H), 0.99 – 0.84 (m, 2H). | C | 785.4 | 785.4 |
| **A145** | 1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.72 (d, J = 8.2 Hz, 1H), 8.39 (s, 4H), 8.31 (d, J = 2.8 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.14 (d, J = 3.6 Hz, 3H), 6.75 (d, J = 3.6 Hz, 2H), 6.68 – 6.58 (m, 5H), 6.37 (d, J = 8.6 Hz, 2H), 6.31 – 6.25 (m, 2H), 5.32 (t, J = 4.6 Hz, 2H), 4.75 (d, J = 12.8 Hz, 1H), 4.32 (t, J = 11.2 Hz, 1H), 4.16 (d, J = 4.2 Hz, 2H), 3.91 – 3.83 (m, 2H), 3.33 – 3.31 (m, 3H), 3.06 (s, 3H), 2.77 (d, J = 11.4 Hz, 1H), 2.33 (s, 2H), 2.15 (d, J | E | 771.4 | 771.4 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | = 12.4 Hz, 1H), 1.94 (d, J = 13.0 Hz, 2H), 1.62 – 1.59 (m, 2H), 1.45 (s, 1H), 1.28 (s, 2H), 0.85 (d, J = 7.2 Hz, 2H). | | | |
| **A146** | 1H NMR (400 MHz, CD3OD_SPE) δ 8.43 (s, 1H), 7.38 (q, 2H), 7.14 – 7.09 (m, 3H), 6.73 – 6.65 (m, 5H), 6.47 (d, J = 8.6 Hz, 2H), 6.34 (d, J = 2.2 Hz, 1H), 6.30 (dd, 1H), 5.12 (dd, 1H), 4.64 – 4.56 (m, 3H), 4.42 (dt, J = 11.0, 8.5 Hz, 3H), 4.22 – 4.12 (m, 2H), 4.09 – 4.02 (m, 1H), 3.57 (t, J = 8.2 Hz, 1H), 3.52 – 3.43 (m, 1H), 3.12 (s, 4H), 2.87 – 2.74 (m, 4H), 2.65 – 2.44 (m, 3H), 2.20 – 2.08 (m, 4H), 1.90 (d, J = 13.4 Hz, 2H), 1.82 – 1.63 (m, 4H), 1.49 (dd, 1H), 1.30 (d, J = 18.0 Hz, 1H). | D | 809.4 | 809.5 |
| **A147** | 1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.27 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 8.18 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.19 – 7.07 (m, 3H), 6.79 – 6.73 (m, 2H), 6.65 (t, J = 8.4 Hz, 1H), 6.61 (d, J = 8.6 Hz, 2H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.22 (m, 2H), 4.76 – 4.64 (m, 1H), 4.47 – 4.41 (m, 1H), 4.31 (d, J = 11.0 Hz, 1H), 4.17 (t, J = 6.0 Hz, 2H), 4.11 – 4.04 (m, 1H), 3.87 (t, J = 7.8 Hz, 1H), 3.77 (d, J = 12.4 Hz, 1H), 3.57 – 3.42 (m, 3H), 3.20 (s, 1H), 3.05 (d, J = 5.6 Hz, 3H), 2.94 (d, J = 10.0 Hz, 1H), 2.82 – 2.72 (m, 2H), 2.68 – 2.55 (m, 1H), 2.35 (d, J = 7.0 Hz, 2H), 2.21 – 2.08 (m, 2H), 2.00 – 1.93 (m, 2H), 1.74 (t, J = 11.0 Hz, 1H), 1.65 – 1.53 (m, 4H), 1.35 (d, J = 12.0 Hz, 1H), 1.24 (s, 2H). | E | 799.4 | 799.5 |
| **A148** | 1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.28 (s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.15 – 7.07 (m, 3H), 6.80 – 6.71 (m, 2H), 6.66 (d, J = 8.2 Hz, 1H), 6.60 (s, 2H), 6.37 (d, | E | 799.4 | 799.5 |

| Compound No | 1HNMR | LCMS method | Calcd. (M+H)+ | Found. (M+H)+ |
|---|---|---|---|---|
| | J = 8.6 Hz, 2H), 6.31 – 6.22 (m, 2H), 4.79 – 4.62 (m, 1H), 4.43 (dd, 2.8 Hz, 1H), 4.32 (t, J = 10.8 Hz, 1H), 4.17 (t, J = 6.2 Hz, 2H), 4.12 – 4.01 (m, 1H), 3.87 (t, J = 7.8 Hz, 1H), 3.77 (d, J = 11.0 Hz, 1H), 3.56 – 3.42 (m, 3H), 3.19 (s, 1H), 3.06 (s, 3H), 2.94 (s, 1H), 2.82 – 2.74 (m, 2H), 2.41 – 2.32 (m, 3H), 2.19 – 2.05 (m, 2H), 2.04 – 1.91 (m, 3H), 1.76 – 1.68 (m, 1H), 1.58 (d, J = 13.6 Hz, 3H), 1.37 – 1.32 (m, 1H), 1.24 (s, 2H). | | | |
| **A149** | 1H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 7.10 (s, 3H), 6.95 (d, J = 6.8 Hz, 2H), 6.69 – 6.54 (m, 5H), 6.48 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 8.4 Hz, 1H), 6.30 – 6.22 (m, 2H), 6.17 (s, 1H), 5.64 (d, J = 6.4 Hz, 1H), 4.64 – 4.57 (m, 1H), 4.34 – 4.19 (m, 2H), 4.04 (d, J = 9.6 Hz, 1H), 3.65 – 3.54 (m, 3H), 3.47 – 3.39 (m, 2H), 3.02 (s, 3H), 2.93 (d, J = 10.4 Hz, 2H), 2.78 – 2.67 (m, 1H), 2.60 – 2.53 (m, 3H), 2.36 – 2.26 (m, 1H), 2.21 – 2.06 (m, 3H), 2.01 – 1.92 (m, 2H), 1.80 – 1.72 (m, 2H), 1.70 – 1.52 (m, 5H), 1.23 – 1.08 (m, 2H). | B | 715.4 | 715.4 |
| **A150** | 1H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 7.14 – 7.04 (m, 3H), 6.95 (d, J = 8.4 Hz, 2H), 6.72 – 6.65 (m, 2H), 6.63 – 6.54 (m, 3H), 6.48 (d, J = 8.4 Hz, 1H), 6.40 – 6.31 (m, 1H), 6.29 – 6.22 (m, 2H), 6.17 (d, J = 2.0 Hz, 1H), 5.64 (d, J = 7.2 Hz, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.34 – 4.22 (m, 2H), 4.07 – 4.00 (m, 1H), 3.62 – 3.55 (m, 2H), 3.49 – 3.38 (m, 2H), 3.02 (s, 3H), 2.94 (d, J = 10.4 Hz, 2H), 2.78 – 2.67 (m, 1H), 2.61 – 2.53 (m, 3H), 2.36 – 2.28 (m, 1H), 2.19 (d, J = 6.8 Hz, 2H), 2.13 – 2.06 (m, 1H), 1.98 (t, J = 10.8 Hz, 2H), 1.90 – 1.82 (m, 1H), 1.79 – 1.72 (m, 2H), 1.71 – 1.55 (m, 5H), 1.25 – 1.08 (m, 2H). | B | 715.4 | 715.4 |

| Compound No | [1]HNMR | LCMS method | Calcd. (M+H)+ | Found. (M+H)+ |
|---|---|---|---|---|
| **A151** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.28 (s, 1H), 7.18 – 7.12 (m, 3H), 7.05 (s, 1H), 6.93 (s, 1H), 6.77 – 6.72 (m, 2H), 6.65 – 6.56 (m, 3H), 6.37 (d, J = 8.8 Hz, 2H), 6.33 – 6.23 (m, 2H), 5.09 – 4.98 (m, 1H), 4.37 – 4.23 (m, 4H), 4.16 – 4.10 (m, 2H), 3.93 – 3.78 (m, 4H), 3.51 (d, J = 4.6 Hz, 1H), 3.40 (d, J = 18.2 Hz, 2H), 3.16 (s, 2H), 3.06 (s, 3H), 2.89 (t, J = 12.8 Hz, 2H), 2.73 (d, J = 11.8 Hz, 1H), 2.58 (d, J = 6.8 Hz, 1H), 2.35 (s, 2H), 2.09 (d, J = 10.2 Hz, 1H), 2.01 – 1.88 (m, 3H), 1.74 (t, J = 10.8 Hz, 1H), 1.62 (s, 3H), 1.38 – 1.28 (m, 2H), 1.24 – 1.22 (m, 1H). | E | 810.4 | 810.5 |
| **A152** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.28 (s, 1H), 7.16 – 7.09 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.76 – 6.69 (m, 2H), 6.67 – 6.57 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.31 – 6.22 (m, 2H), 5.09 – 4.95 (m, 1H), 4.33 – 4.23 (m, 3H), 4.18 – 4.08 (m, 3H), 3.92 – 3.79 (m, 3H), 3.55 – 3.39 (m, 3H), 3.14 (s, 1H), 3.06 (s, 3H), 2.91 (d, J = 12.6 Hz, 2H), 2.74 (d, J = 9.0 Hz, 1H), 2.61 – 2.55 (m, 2H), 2.35 (d, J = 12.4 Hz, 3H), 2.18 – 2.07 (m, 1H), 1.97 – 1.89 (m, 2H), 1.79 – 1.68 (m, 1H), 1.60 – 1.55 (m, 2H), 1.31 (s, 1H), 1.24 (s, 1H). | B | 810.4 | 810.4 |
| **A153** | 1H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 7.45 (s, 1H), 7.22 – 7.08 (m, 3H), 7.00 (s, 1H), 6.81 – 6.71 (m, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.37 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.07 (dd, J = 13.2, 5.2 Hz, 1H), 4.48 – 4.40 (m, 2H), 4.38 – 4.28 (m, 2H), 4.24 – 4.11 (m, 3H), 3.54 – 3.44 (m, 2H), 3.41 – 3.39 (m, 2H), 3.36 – 3.33 (m, 2H), 2.97 – 2.77 (m, 3H), 2.64 – 2.54 (m, 1H), 2.42 – 2.30 (m, 1H), 2.11 (d, J = 6.8 Hz, 2H), 1.99 – 1.80 (m, 7H), 1.73 – 1.63 (m, 4H), | C | 793.4 | 793.4 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 1.53 – 1.38 (m, 3H), 0.98 – 0.83 (m, 2H). | | | |
| **A154** | 1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.26 (s, 1H), 7.42 – 7.22 (m, 2H), 7.18 – 7.07 (m, 3H), 6.79 – 6.72 (m, 2H), 6.70 – 6.58 (m, 1H), 6.36 – 6.25 (m, 4H), 6.12 – 6.06 (m, 2H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.51 (s, 2H), 4.40 – 4.29 (m, 2H), 4.24 – 4.13 (m, 3H), 3.52 – 3.46 (m, 1H), 3.44 – 3.37 (m, 2H), 3.38 – 3.34 (m, 2H), 2.99 – 2.73 (m, 3H), 2.63 – 2.56 (m, 1H), 2.46 – 2.27 (m, 1H), 2.18 – 2.06 (m, 2H), 2.02 – 1.79 (m, 6H), 1.74 – 1.64 (m, 3H), 1.53 – 1.37 (m, 3H), 1.28 – 1.21 (m, 2H), 0.98 – 0.83 (m, 2H). | C | 793.4 | 793.5 |
| **A155** | 1H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 8.16 (s, 1H), 7.12 (d, J = 7.0 Hz, 3H), 7.01 (d, J = 8.2 Hz, 2H), 6.76 (d, J = 6.2 Hz, 2H), 6.67 – 6.62 (m, 3H), 6.60 – 6.57 (m, 2H), 6.38 – 6.23 (m, 3H), 5.84 (d, J = 7.6 Hz, 1H), 4.46 (d, J = 5.0 Hz, 1H), 4.33 (dd, J = 21.6, 10.5 Hz, 2H), 4.14 (d, J = 7.7 Hz, 1H), 3.84 (dd, J = 15.4, 7.8 Hz, 1H), 3.12 (s, 5H), 3.00 (d, J = 9.8 Hz, 1H), 2.80 – 2.64 (m, 2H), 2.31 (d, J = 7.3 Hz, 4H), 2.11 (s, 5H), 2.04 – 1.94 (m, 2H), 1.88 (d, J = 12.6 Hz, 3H), 1.62 – 1.56 (m, 3H), 1.28 – 1.20 (m, 1H), 0.85 (d, J = 7.0 Hz, 1H). | B | 828.4 | 828.5 |
| **A156** | 1H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 8.27 (s, 1H), 7.13 – 7.10 (m, 3H), 7.01 (d, J = 8.2 Hz, 2H), 6.76 (d, J = 6.0 Hz, 2H), 6.68 – 6.60 (m, 4H), 6.59 (d, J = 4.4 Hz, 2H), 6.38 – 6.24 (m, 3H), 5.84 (d, J = 7.4 Hz, 1H), 4.46 (d, J = 5.2 Hz, 1H), 4.39 – 4.25 (m, 2H), 4.14 (d, J = 8.2 Hz, 1H), 3.88 – 3.79 (m, 1H), 3.52 (d, J = 10.6 Hz, 2H), 3.00 (d, J = 10.4 Hz, 1H), 2.80 – 2.64 (m, 2H), 2.36 – 2.25 (m, 3H), 2.19 – 2.04 (m, 5H), 2.04 – 1.95 | B | 807.4 | 807.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. $(M+H)^{+}$ | Found. $(M+H)^{+}$ |
|---|---|---|---|---|
| | (m, 1H), 1.94 – 1.80 (m, 3H), 1.62 – 1.57 (m, 2H), 1.36 – 1.19 (m, 5H), 0.88 – 0.82 (m, 1H). | | | |
| **A157** | 1H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.29 (s, 1H), 7.19 – 7.15 (m, 1H), 7.14 – 7.08 (m, 3H), 7.01 (d, J = 8.6 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 – 6.26 (m, 3H), 5.06 – 4.99 (m, 1H), 4.46 (d, J = 5.2 Hz, 1H), 4.38 – 4.22 (m, 3H), 4.17 – 4.06 (m, 2H), 3.99 – 3.78 (m, 3H), 3.56 – 3.48 (m, 2H), 3.16 – 3.08 (m, 5H), 3.04 – 2.98 (m, 1H), 2.94 – 2.84 (m, 2H), 2.76 – 2.66 (m, 2H), 2.39 – 2.32 (m, 3H), 2.17 – 2.04 (m, 1H), 2.00 – 1.90 (m, 2H), 1.82 – 1.70 (m, 1H), 1.68 – 1.53 (m, 4H), 1.38 – 1.30 (m, 1H). | B | 828.4 | 828.4 |
| **A158** | 1H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.29 (s, 1H), 7.19 – 7.15 (m, 1H), 7.14 – 7.08 (m, 3H), 7.01 (d, J = 8.6 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 – 6.26 (m, 3H), 5.06 – 4.99 (m, 1H), 4.46 (d, J = 5.2 Hz, 1H), 4.38 – 4.22 (m, 3H), 4.17 – 4.06 (m, 2H), 3.99 – 3.78 (m, 3H), 3.56 – 3.48 (m, 2H), 3.16 – 3.08 (m, 5H), 3.04 – 2.98 (m, 1H), 2.94 – 2.84 (m, 2H), 2.76 – 2.66 (m, 2H), 2.39 – 2.32 (m, 3H), 2.17 – 2.04 (m, 1H), 2.00 – 1.90 (m, 2H), 1.82 – 1.70 (m, 1H), 1.68 – 1.53 (m, 4H), 1.38 – 1.30 (m, 1H). | B | 828.4 | 828.4 |
| **A159** | 1H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 9.29 (s, 1H), 8.17 (s, 1H), 7.14 – 7.09 (m, 3H), 7.01 (d, J = 8.0 Hz, 2H), 6.78 – 6.74 (m, 2H), 6.64 (t, J = 8.8 Hz, 3H), 6.60 – 6.57 (m, 2H), 6.37 – 6.32 (m, 1H), 6.31 – 6.26 (m, 2H), 5.84 (d, J = 7.4 Hz, 1H), 4.46 (d, J = 5.4 Hz, 1H), 4.37 – 4.26 (m, 2H), 4.18 – 4.11 (m, 1H), 3.87 – 3.80 (m, | C | 806.4 | 806.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. $(M+H)^+$ | Found. $(M+H)^+$ |
|---|---|---|---|---|
| | 1H), 3.55 – 3.50 (m, 1H), 3.44 – 3.42 (m, 1H), 3.14 – 3.11 (m, 3H), 2.69 – 2.66 (m, 3H), 2.33 – 2.31 (m, 2H), 2.16 – 2.06 (m, 5H), 1.93 – 1.84 (m, 3H), 1.82 – 1.77 (m, 1H), 1.63 – 1.53 (m, 5H), 1.35 – 1.28 (m, 1H). | | | |
| **A160** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.27 (s, 1H), 7.14 – 7.09 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.78 – 6.74 (m, 2H), 6.66 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 (s, 1H), 6.33 (s, 1H), 6.32 – 6.28 (m, 2H), 6.28 – 6.26 (m, 1H), 5.02 (dd, J = 13.4, 5.0 Hz, 1H), 4.46 (d, J = 5.0 Hz, 1H), 4.38 – 4.25 (m, 3H), 4.22 (s, 1H), 4.18 – 4.10 (m, 2H), 3.93 – 3.85 (m, 2H), 3.84 – 3.77 (m, 1H), 3.18 – 3.08 (m, 6H), 3.06 – 2.83 (m, 4H), 2.76 (s, 2H), 2.37 – 2.32 (m, 3H), 2.13 – 2.04 (m, 1H), 2.01 – 1.89 (m, 3H), 1.72 – 1.57 (m, 5H), 1.38 – 1.31 (m, 1H). | C | 828.4 | 828.5 |
| **A161** | 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.27 (s, 1H), 7.14 – 7.09 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.78 – 6.74 (m, 2H), 6.66 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 (s, 1H), 6.33 (s, 1H), 6.32 – 6.28 (m, 2H), 6.28 – 6.26 (m, 1H), 5.02 (dd, J = 13.4, 5.0 Hz, 1H), 4.46 (d, J = 5.0 Hz, 1H), 4.38 – 4.25 (m, 3H), 4.22 (s, 1H), 4.18 – 4.10 (m, 2H), 3.93 – 3.85 (m, 2H), 3.84 – 3.77 (m, 1H), 3.18 – 3.08 (m, 6H), 3.06 – 2.83 (m, 4H), 2.76 (s, 2H), 2.37 – 2.32 (m, 3H), 2.13 – 2.04 (m, 1H), 2.01 – 1.89 (m, 3H), 1.72 – 1.57 (m, 5H), 1.38 – 1.31 (m, 1H). | C | 828.4 | 828.5 |
| **A162** | $^1$H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.58 (m, 3H), 6.46 – 6.34 (m, 4H), 6.33 – 6.25 (m, 2H), 5.98 (d, *J* = 7.6 Hz, 1H), 4.36 – | B | 759.4 | 759.5 |

| Compound No | $^1$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| | 4.27 (m, 2H), 4.20 – 4.14 (m, 2H), 3.84 (d, *J* = 7.2 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.42 (d, *J* = 6.0 Hz, 1H), 3.09 – 3.03 (m, 4H), 2.95 – 2.90 (m, 1H), 2.76 – 2.69 (m, 1H), 2.59 – 2.55 (m, 2H), 2.33 (d, *J* = 7.2 Hz, 2H), 2.10 – 1.83 (m, 6H), 1.73 – 1.49 (m, 9H), 1.32 (dd, *J* = 12.4, 8.0 Hz, 1H). | | | |
| **A163** | $^1$H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.58 (m, 3H), 6.46 – 6.34 (m, 4H), 6.33 – 6.25 (m, 2H), 5.98 (d, *J* = 7.6 Hz, 1H), 4.36 – 4.27 (m, 2H), 4.20 – 4.14 (m, 2H), 3.84 (d, *J* = 7.2 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.42 (d, *J* = 6.0 Hz, 1H), 3.09 – 3.03 (m, 4H), 2.95 – 2.90 (m, 1H), 2.76 – 2.69 (m, 1H), 2.59 – 2.55 (m, 2H), 2.33 (d, *J* = 7.2 Hz, 2H), 2.10 – 1.83 (m, 6H), 1.73 – 1.49 (m, 9H), 1.32 (dd, *J* = 12.4, 8.0 Hz, 1H). | B | 759.4 | 759.5 |
| **A164** | $^1$H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.58 (m, 3H), 6.46 – 6.34 (m, 4H), 6.33 – 6.25 (m, 2H), 5.98 (d, *J* = 7.6 Hz, 1H), 4.36 – 4.27 (m, 2H), 4.20 – 4.14 (m, 2H), 3.84 (d, *J* = 7.2 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.42 (d, *J* = 6.0 Hz, 1H), 3.09 – 3.03 (m, 4H), 2.95 – 2.90 (m, 1H), 2.76 – 2.69 (m, 1H), 2.59 – 2.55 (m, 2H), 2.33 (d, *J* = 7.2 Hz, 2H), 2.10 – 1.83 (m, 6H), 1.73 – 1.49 (m, 9H), 1.32 (dd, *J* = 12.4, 8.0 Hz, 1H). | B | 759.4 | 759.5 |
| **A165** | $^1$H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.58 (m, 3H), 6.46 – 6.34 (m, 4H), 6.33 – 6.25 (m, 2H), 5.98 (d, *J* = 7.6 Hz, 1H), 4.36 – 4.27 (m, 2H), 4.20 – 4.14 (m, 2H), 3.84 (d, *J* = 7.2 Hz, 1H), 3.52 – 3.48 | B | 759.4 | 759.5 |

| Compound No | $^{1}$HNMR | LCMS method | Calcd. (M+H)$^+$ | Found. (M+H)$^+$ |
|---|---|---|---|---|
| | (m, 1H), 3.42 (d, *J* = 6.0 Hz, 1H), 3.09 – 3.03 (m, 4H), 2.95 – 2.90 (m, 1H), 2.76 – 2.69 (m, 1H), 2.59 – 2.55 (m, 2H), 2.33 (d, *J* = 7.2 Hz, 2H), 2.10 – 1.83 (m, 6H), 1.73 – 1.49 (m, 9H), 1.32 (dd, *J* = 12.4, 8.0 Hz, 1H). | | | |

**FOR COMPOUNDS B1 to B5**

**Table 5. Characterization Data for Compounds B1 to B5**

| Compound No | LC-MS ([M+H]$^+$) |
|---|---|
| **B1** | 754.36 |
| **B2** | 794.31 |
| **B3** | 794.33 |
| **B4** | 793.31 |
| **B5** | 794.3 |

## II. BIOLOGICAL ASSAYS FOR COMPOUNDS 1-165

***In vitro* Assay: $IC_{50}$ Measurements for binding to CRBN/DDB1**

**[0463]** 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. The binding $IC_{50}$ data for compounds are summarized in **Table 6**.

**Table 6. Binding $IC_{50}$ to CRBN/DDB1**

| Compound No. | CRBN HTRF $IC_{50}$ (nM) |
|---|---|
| **A1** | D |
| **A2** | D |
| **A3** | B |
| **A4** | C |
| **A5** | C |
| **A6** | B |
| **A7** | B |
| **A8** | B |
| **A9** | B |
| **A10** | C |
| **A11** | D |
| **A12** | B |
| **A13** | B |
| **A14** | C |
| **A15** | B |
| **A16** | B |
| **A17** | B |
| **A18** | C |
| **A19** | B |

| Compound No. | CRBN HTRF $IC_{50}$ (nM) |
|---|---|
| **A20** | A |
| **A21** | A |
| **A22** | A |
| **A23** | A |
| **A24** | A |
| **A25** | B |
| **A26** | B |
| **A27** | C |
| **A28** | D |
| **A29** | C |
| **A30** | C |
| **A31** | B |
| **A32** | C |
| **A33** | A |
| **A34** | B |
| **A35** | B |
| **A36** | B |
| **A37** | A |
| **A38** | B |
| **A39** | B |
| **A40** | B |
| **A41** | B |
| **A42** | B |
| **A43** | D |
| **A44** | B |
| **A45** | B |
| **A46** | C |
| **A47** | C |
| **A48** | B |
| **A49** | B |
| **A50** | B |
| **A51** | C |
| **A52** | B |
| **A53** | C |

| Compound No. | CRBN HTRF $IC_{50}$ (nM) |
|---|---|
| A54 | C |
| A55 | C |
| A56 | B |
| A57 | D |
| A58 | C |
| A59 | B |
| A60 | B |
| A61 | B |
| A62 | B |
| A63 | C |
| A64 | B |
| A65 | B |
| A67 | B |
| A69 | B |
| A70 | B |
| A71 | B |
| A72 | B |
| A73 | A |
| A74 | C |
| A75 | B |
| A76 | B |
| A77 | C |
| A78 | C |
| A79 | C |
| A80 | C |
| A81 | C |
| A82 | C |
| A83 | D |
| A84 | C |
| A85 | D |
| A86 | B |
| A87 | D |
| A88 | D |
| A89 | A |

| Compound No. | CRBN HTRF $IC_{50}$ (nM) |
|---|---|
| A90 | D |
| A91 | D |
| A92 | D |
| A93 | C |
| A94 | C |
| A95 | C |
| A96 | B |
| A97 | C |
| A98 | B |
| A99 | B |
| A100 | D |
| A101 | D |
| A102 | C |
| A103 | C |
| A104 | C |
| A105 | A |
| A106 | A |
| A107 | D |
| A108 | C |
| A109 | D |
| A110 | D |
| A111 | C |
| A112 | D |
| A113 | A |
| A114 | A |
| A115 | B |
| A116 | C |
| A117 | C |
| A118 | C |
| A119 | C |
| A120 | C |
| A121 | C |
| A122 | B |
| A123 | B |

| Compound No. | CRBN HTRF $IC_{50}$ (nM) |
|---|---|
| **A124** | D |
| **A125** | B |
| **A126** | A |
| **A127** | D |
| **A128** | D |
| **A129** | D |
| **A130** | B |
| **A131** | A |
| **A132** | A |
| **A133** | A |
| **A134** | C |
| **A135** | A |
| **A136** | A |
| **A137** | A |
| **A138** | B |
| **A139** | C |
| **A140** | C |
| **A141** | B |
| **A142** | C |
| **A144** | C |
| **A145** | D |
| **A146** | A |
| **A147** | C |
| **A148** | C |
| **A149** | B |
| **A150** | B |
| **A151** | B |
| **A152** | B |
| **A153** | B |
| **A154** | A |
| **A155** | A |
| **A156** | C |
| **A157** | A |
| **A158** | A |

| Compound No. | CRBN HTRF $IC_{50}$ (nM) |
|---|---|
| **A159** | C |
| **A160** | C |
| **A161** | B |
| **A162** | A |
| **A163** | B |
| **A164** | A |
| **A165** | B |

**Note: $IC_{50}$: "A": < 50 nM; "B": 50-500 nM; "C": > 500 and <5000 nM; "D": >=5000 nM.**

***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
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:*

**[0464]** Prepare complete nuclear receptor buffer K 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. Prepare 2X protein solution using complete nuclear receptor buffer K containing 8nM

ERα_LBD(GST) and 4nM Tb Anti-GST. Then, prepare 2X Fluormone ES2 Green tracer (6 nM) 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, add 6 μL 2X protein solution into the plate. Briefly and gently mix the 384-well plate on a plate shaker and incubate at room temperature protected from light for 60min. The plate is sealed with a cover to minimize evaporation. Read the plate at wavelengths of 520 nm and 495 nm. Calculate the TR-FRET ratio by dividing the emission signal at 520 nm by the emission signal at 495 nm. Generate a binding curve 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. The ERα binding $IC_{50}$ data are summarized in **Table 7**.

**Table 7. ERα binding $IC_{50}$**

| Compound No | ERα HTRF $IC_{50}$ (nM) |
|---|---|
| **A8** | A |
| **A9** | A |
| **A21** | A |
| **A22** | |
| **A23** | |
| **A24** | |
| **A25** | |
| **A26** | A |
| **A27** | A |
| **A35** | A |
| **A36** | |
| **A37** | |
| **A38** | |
| **A39** | |
| **A40** | B |
| **A41** | B |
| **A44** | A |
| **A49** | A |
| **A50** | A |
| **A53** | A |
| **A56** | A |

| Compound No | ERα HTRF $IC_{50}$ (nM) |
|---|---|
| **A58** | A |
| **A59** | A |
| **A62** | A |
| **A64** | A |
| **A66** | B |
| **A68** | A |
| **A77** | A |
| **A78** | |
| **A79** | |
| **A80** | |
| **A81** | A |
| **A84** | A |
| **A99** | A |
| **A106** | A |
| **A110** | A |
| **A113** | A |
| **A114** | A |
| **A115** | A |
| **A117** | A |
| **A118** | A |
| **A120** | A |
| **A121** | A |
| **A122** | A |
| **A125** | A |
| **A130** | A |
| **A132** | A |
| **A137** | A |
| **A138** | A |
| **A140** | A |
| **A142** | A |
| **A145** | A |
| **A146** | B |
| **A147** | A |
| **A150** | A |

| Compound No | ERα HTRF $IC_{50}$ (nM) |
|---|---|
| **A153** | A |
| **A154** | A |

Note: $IC_{50}$: "A": < 5 nM; "B": >=5 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

- *Procedures for ICW assays*

In vitro Assay: MCF-7 and T47D ICW assay

**[0465]** Day1: 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.

**[0466]** 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.

**[0467]** Day 3: After 16 hrs of compounds treatment, cells were fixed by 4% PFA and

**[0468]** 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.

**[0469]** 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*

**[0470]** Data are analyzed by image studio V5.2 and XLfit.

**[0471]** Half maximal degradation concentration values ($DC_{50}$) and maximal degradation percentage ($D_{max}$, %) of ER are summarized in **Table 8**.

**Table 8. 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 | B | | |
| **A2** | B | B | | |
| **A3** | B | C | | |
| **A6** | B | B | | |
| **A7** | B | B | | |
| **A8** | B | B | | |
| **A9** | B | B | | |
| **A14** | B | C | | |
| **A16** | A | B | | |
| **A17** | A | B | | |
| **A27** | B | B | | |
| **A33** | B | B | B | B |
| **A34** | B | C | | |
| **A35** | B | C | B | B |
| **A36** | C | C | | |
| **A37** | B | C | | |

| Compound No | MCF7 $DC_{50}$ (nM) | MCF7 $D_{max}$ % | T47D $DC_{50}$ (nM) | T47D $D_{max}$ % |
|---|---|---|---|---|
| **A38** | C | C | | |
| **A39** | D | D | | |
| **A40** | B | B | A | B |
| **A41** | B | B | A | A |
| **A42** | D | D | | |
| **A43** | D | D | | |
| **A44** | B | B | A | B |
| **A45** | D | D | | |
| **A46** | D | D | | |
| **A47** | C | C | | |
| **A48** | D | D | | |
| **A49** | B | B | B | B |
| **A50** | B | B | A | B |
| **A51** | A | C | A | C |
| **A52** | D | D | A | C |
| **A53** | B | B | B | A |
| **A54** | C | C | B | A |
| **A55** | D | D | D | D |
| **A56** | B | B | A | A |
| **A57** | D | D | D | D |
| **A58** | B | C | B | B |
| **A59** | B | B | A | A |
| **A60** | A | C | B | D |
| **A61** | B | C | B | B |
| **A62** | A | B | A | B |
| **A63** | D | D | D | D |
| **A64** | B | C | B | B |
| **A65** | B | D | B | C |

| Compound No | MCF7 $DC_{50}$ (nM) | MCF7 $D_{max}$ % | T47D $DC_{50}$ (nM) | T47D $D_{max}$ % |
|---|---|---|---|---|
| **A66** | B | B | B | B |
| **A67** | D | D | C | D |
| **A68** | B | B | B | A |
| **A69** | B | D | B | C |
| **A70** | D | D | B | C |
| **A71** | A | B | A | B |
| **A72** | D | D | A | C |
| **A73** | A | B | A | B |
| **A74** | A | D | B | C |
| **A75** | A | C | B | B |
| **A76** | | | D | D |
| **A77** | A | B | A | B |
| **A78** | | | C | C |
| **A79** | A | A | A | A |
| **A80** | | | C | B |
| **A81** | A | A | A | A |
| **A82** | | | B | C |
| **A83** | | | D | D |
| **A84** | A | B | A | B |
| **A85** | A | B | B | B |
| **A86** | | | A | C |
| **A87** | | | B | C |
| **A88** | B | B | B | B |
| **A89** | A | A | A | A |
| **A90** | B | B | A | B |
| **A91** | B | B | B | B |
| **A92** | A | B | A | B |
| **A93** | B | B | A | B |

| Compound No | MCF7 $DC_{50}$ (nM) | MCF7 $D_{max}$ % | T47D $DC_{50}$ (nM) | T47D $D_{max}$ % |
|---|---|---|---|---|
| **A94** | | | B | B |
| **A95** | B | B | B | B |
| **A96** | A | B | A | B |
| **A97** | | | A | C |
| **A98** | A | A | A | A |
| **A99** | A | B | A | B |
| **A100** | B | B | B | B |
| **A101** | | | A | D |
| **A102** | A | B | | |
| **A103** | B | B | B | B |
| **A104** | B | A | B | A |
| **A105** | C | C | B | C |
| **A106** | A | A | A | A |
| **A107** | B | C | A | C |
| **A108** | B | B | A | A76.29 |
| **A109** | C | C | B | C |
| **A110** | A | B | A | B |
| **A111** | A | B | A | B |
| **A112** | D | D | B | D |
| **A113** | A | B | A | B |
| **A114** | A | A | A | A |
| **A115** | A | A | A | A |
| **A116** | A | B | A | B |
| **A117** | A | A | A | A |
| **A118** | B | A | B | A |
| **A119** | B | B | B | B |
| **A120** | B | A | A | A |
| **A121** | A | A | A | A |

| Compound No | MCF7 $DC_{50}$ (nM) | MCF7 $D_{max}$ % | T47D $DC_{50}$ (nM) | T47D $D_{max}$ % |
|---|---|---|---|---|
| **A122** | A | A | A | A |
| **A123** | A | B | A | B |
| **A124** | A | B | A | B |
| **A125** | A | A | A | A |
| **A126** | B | C | A | B |
| **A127** | A | B | A | C |
| **A128** | A | B | A | B |
| **A129** | C | C | C | B |
| **A130** | A | A | A | A |
| **A131** | B | B | B | B |
| **A132** | B | B | B | B |
| **A133** | B | C | A | C |
| **A134** | A | A | A | A |
| **A135** | A | C | A | C |
| **A136** | A | B | A | B |
| **A137** | A | B | A | B |
| **A138** | A | A | A | B |
| **A139** | A | B | A | B |
| **A140** | A | B | A | B |
| **A141** | B | B | B | B |
| **A142** | B | B | A | B |
| **A143** | C | C | C | C |
| **A144** | C | C | D | D |
| **A145** | B | B | A | B |
| **A146** | B | B | B | C |
| **A147** | A | B | A | B |
| **A148** | A | B | A | B |
| **A149** | A | B | A | B |

| Compound No | MCF7 $DC_{50}$ (nM) | MCF7 $D_{max}$ % | T47D $DC_{50}$ (nM) | T47D $D_{max}$ % |
|---|---|---|---|---|
| **A150** | A | C | A | C |
| **A151** | A | B | A | B |
| **A152** | C | B | B | B |
| **A153** | A | B | A | A |
| **A154** | A | B | A | A |
| **A155** | D | D | B | C |
| **A156** | D | D | A | C |
| **A157** | A | B | A | A |
| **A158** | A | B | A | A |
| **A159** | B | C | B | B |
| **A160** | B | D | B | C |
| **A161** | A | B | A | A |
| **A162** | A | C | A | A |
| **A163** | A | C | A | B |
| **A164** | A | C | B | B |
| **A165** | 0.31 | C | A | B |

**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

**[0472]** 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.

**[0473]** 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.

**[0474]** Day 0 and Day 6: add Cell TiterGlo reagent and read on EnVision after 30min incubation for data generation.

- *Data analysis*

**[0475]** Data are analyzed by image studio V5.2 and XLfit.

**[0476]** The $IC_{50}$ data on day 6 were summarized in **Table 9**.

**Table 9. CellTiter-Glo® (proliferation) data**

| Compound No. | MCF7 Proliferation $IC_{50}$ (nM) | T47D Proliferation $IC_{50}$ (nM) |
|---|---|---|
| **A50** | B | B |
| **A51** | B | B |
| **A53** | B | B |
| **A56** | A | A |
| **A58** | B | B |
| **A59** | B | B |
| **A62** | A | A |
| **A92** | A | A |
| **A95** | B | A |
| **A96** | A | A |
| **A98** | A | A |
| **A113** | A | D |
| **A114** | A | A |
| **A115** | B | B |
| **A116** | A | B |

| Compound No. | MCF7 Proliferation $IC_{50}$ (nM) | T47D Proliferation $IC_{50}$ (nM) |
|---|---|---|
| **A117** | A | A |
| **A118** | B | B |
| **A119** | B | C |
| **A120** | B | B |
| **A121** | A | B |
| **A122** | A | A |
| **A138** | A | A |
| **A150** | B | B |
| **A154** | A | A |
| **A161** | A | |

**Note: $IC_{50}$: "A": < 50 nM; "B": 50-500 nM; "C": > 500 and <5000 nM; "D": >=5000 nM.**

**FOR COMPOUND B1 to B5**

**[0477] 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%.

**[0478] 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.

**[0479] 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.

**[0480] 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 10.**

| Compound No. | ICW $DC_{50}$ (nM) | Cell Growth Inhibition in T47D cell line $IC_{50}$ (nM) |
|---|---|---|
| **B1** | C | C |
| **B2** | C | C |
| **B3** | C | C |
| **B4** | C | C |
| **B5** | C | C |

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*

**[0481]** 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*

**[0482]** 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*

**[0483]** 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 ($2 \times 10^7$) 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 3$^{rd}$ 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*

**[0484]** 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 $1 \times 10^7$ 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 $^{D}T/^{D}C$ TGI (%) = $(1-((T_e-T_0)/(C_e-C_0))) * 100$, where $^{D}T/^{D}C$ 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

**[0485]** 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

**[0486]** 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.

**[0487]** 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.

WHAT IS CLAIMED IS:

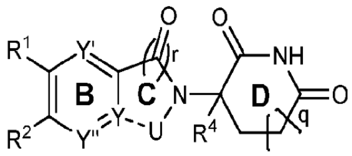
1. A compound of Formula **I**:

**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;

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;

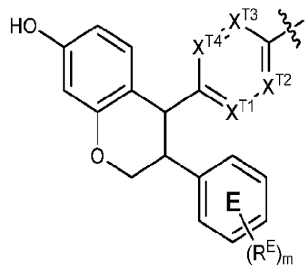
U is $-CH_2-$, -C(=O)-, $-(C=O)-N(R^U)-*$, or $-N=C(R^U)-*$;

$R^U$ 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 $R^E$ 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**:

$$*\text{-}\S\text{-}W-Cy^1\left[Z'\right]_p\S\text{-}** \quad \textbf{(I-3)},$$

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, $C_{3-12}$ membered 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)-, $C_{3-12}$ membered 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,

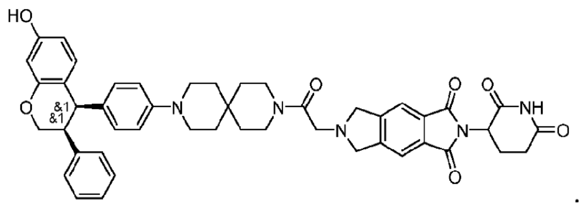
wherein each of $R^a$, $R^b$, $R^c$, and $R^d$ is independently and optionally substituted with one or more $R^z$; and

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.

2. The compound of claim 1, wherein

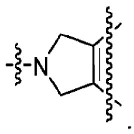
1) when the bond between Y and U is present, U is $-CH_2-$ or -C(=O)-, and r is 1, then either $R^1$ and $R^2$, or $R^2$ and $R^3$, together with the intervening carbon atoms, form Ring A attached to **L**; and

2) the compound is not



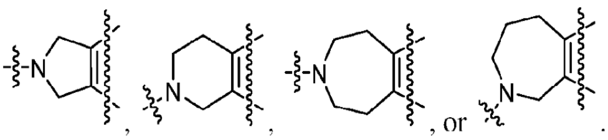
.

3. The compound of claim 1 or 2, wherein 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

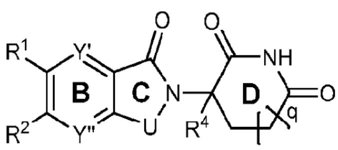


.

4. The compound of any one of claims 1-3, wherein 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



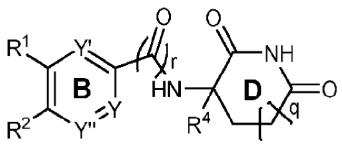
5. The compound of any one of claims 1-4, wherein **C** is of Formula **I-1-i**



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

6. The compound of claim 5, wherein U is $-CH_2-$ or -C(=O)-.

7. The compound of any one of claims 1-4, wherein **C** is of Formula **I-1-ii**



(I-1-ii).

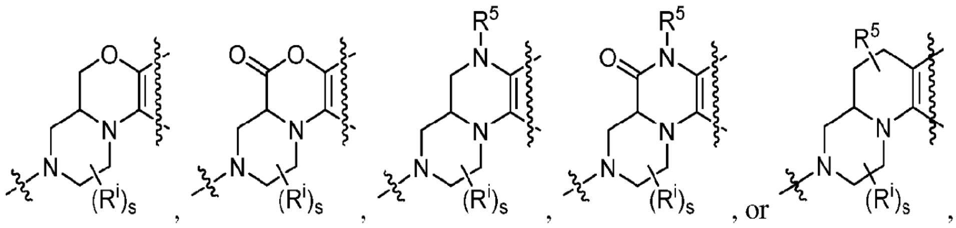
8. The compound of claim 7, wherein Y is N.

9. The compound of claim 7, wherein Y is $CR^Y$, and $R^Y$ is hydrogen, halogen, or $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

10. The compound of any one of claims 1-9, 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.

11. The compound of claim 10, wherein Ring A is optionally substituted 7- to 16-membered fused heterocycle.

12. The compound of claim 11, wherein Ring A is



wherein:

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

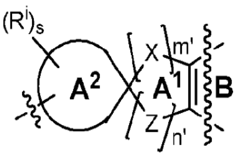
each $R^i$ is independently oxo, halogen, -CN, -$NO_2$, -OH, -$NH_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylamino, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{6-10}$ aryl, 5- to 10-membered heteroaryl, $C_{3-12}$ carbocyclyl, 3- to 12-membered heterocyclyl, -$SR^b$, -$S(=O)R^a$, -$S(=O)_2R^a$,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

13. The compound of claim 10, wherein Ring A is optionally substituted 7- to 16-membered spiro heterocycle.

14. The compound of claim 13, wherein Ring A is:




,

wherein:

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;

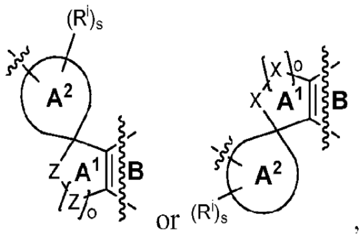
each $R^i$ is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylamino, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{6-10}$ aryl, 5- to 10-membered heteroaryl, $C_{3-12}$ carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$,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

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

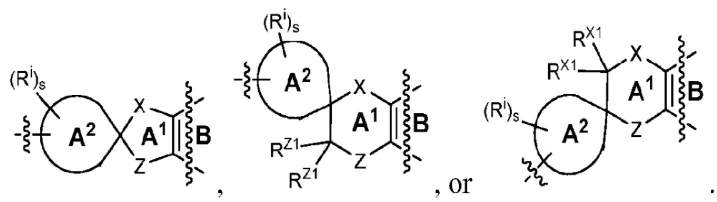
15. The compound of claim 14, wherein Ring A is:

1)



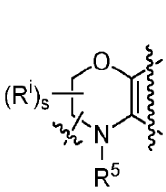
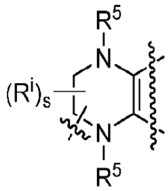
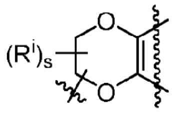
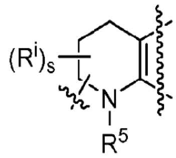
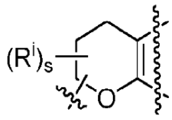
wherein o is 0 or 1; or

2)



16. The compound of claim 10, wherein Ring A is optionally substituted 5- to 6-membered heterocycle.

17. The compound of claim 16, wherein Ring A is

, , ,  or ,

wherein:

$R^5$ 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 10-17, wherein Y" is N.

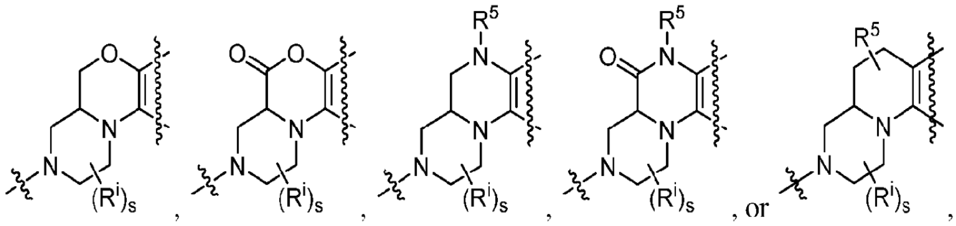
19. The compound of any one of claims 10-17, wherein Y" is $CR^3$, and $R^3$ is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylamino, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{6-10}$ aryl, 5- to 10-membered heteroaryl, $C_{3-12}$ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more $R^u$.

20. The compound of claim 19, wherein $R^3$ is hydrogen, halogen, or $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

21. The compound of any one of claims 1-9, 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.

22. The compound of claim 21, wherein Ring A is optionally substituted 7- to 16-membered fused heterocycle.

23. The compound of claim 22, wherein Ring A is



wherein:

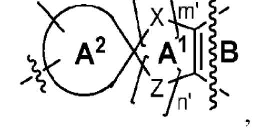
$R^5$ is hydrogen or $C_{1-6}$ alkyl optionally substituted with one or more $R^u$;

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)$_2NR^cR^d$, -$NR^c$S(=O)$_2R^a$, -$NR^c$S(=O)$R^a$, -$NR^c$S(=O)$_2OR^b$, -$NR^c$S(=O)$_2NR^cR^d$, -$NR^b$C(=O)$NR^cR^d$, -$NR^b$C(=O)$R^a$, -$NR^b$C(=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.

24. The compound of claim 21, wherein Ring A is optionally substituted 7- to 16-membered spiro heterocycle.

25. The compound of claim 24, wherein Ring A is:



wherein:

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($R^{Z1}$)$_2$-, -N$R^{Z2}$-, -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, -S$R^b$, -S(=O)$R^a$, -S(=O)$_2R^a$, -S(=O)$_2$O$R^b$, -S(=O)$_2$N$R^cR^d$, -N$R^c$S(=O)$_2R^a$, -N$R^c$S(=O)$R^a$, -N$R^c$S(=O)$_2$O$R^b$, -N$R^c$S(=O)$_2$N$R^cR^d$, -N$R^b$C(=O)N$R^cR^d$, -N$R^b$C(=O)$R^a$, -N$R^b$C(=O)O$R^b$, -OS(=O)$_2R^a$, -OS(=O)$_2$O$R^b$, -OS(=O)$_2$N$R^cR^d$, -OC(=O)$R^a$, -OC(=O)O$R^b$, -OC(=O)N$R^cR^d$, -C(=O)$R^a$, -C(=O)O$R^b$, or -C(=O)N$R^cR^d$, 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;

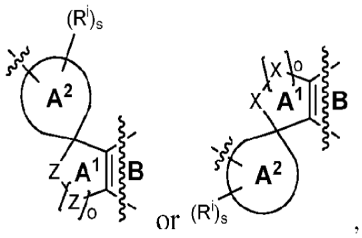
each $R^i$ is independently oxo, halogen, -CN, -$NO_2$, -OH, -$NH_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylamino, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{6-10}$ aryl, 5- to 10-membered heteroaryl, $C_{3-12}$ carbocyclyl, 3- to 12-membered heterocyclyl, -S$R^b$, -S(=O)$R^a$, -S(=O)$_2R^a$, -S(=O)$_2$O$R^b$, -S(=O)$_2$N$R^cR^d$, -N$R^c$S(=O)$_2R^a$, -N$R^c$S(=O)$R^a$, -N$R^c$S(=O)$_2$O$R^b$, -N$R^c$S(=O)$_2$N$R^cR^d$, -N$R^b$C(=O)N$R^cR^d$, -N$R^b$C(=O)$R^a$, -N$R^b$C(=O)O$R^b$, -OS(=O)$_2R^a$, -OS(=O)$_2$O$R^b$, -OS(=O)$_2$N$R^cR^d$, -OC(=O)$R^a$, -OC(=O)O$R^b$, -OC(=O)N$R^cR^d$, -C(=O)$R^a$, -C(=O)O$R^b$, or -C(=O)N$R^cR^d$, 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,

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

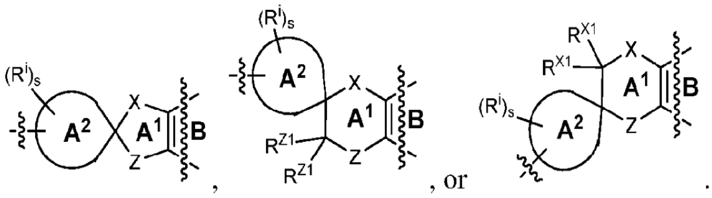
26. The compound of claim 25, wherein Ring A is:

1)



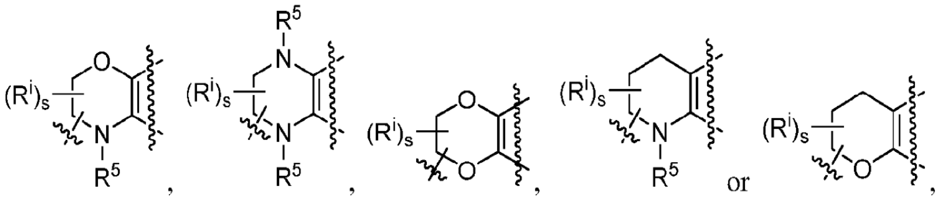
wherein o is 0 or 1; or

2)



27. The compound of claim 21, wherein Ring A is optionally substituted 5- to 6-membered heterocycle.

28. The compound of claim 27, wherein Ring A is



wherein:

$R^5$ 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.

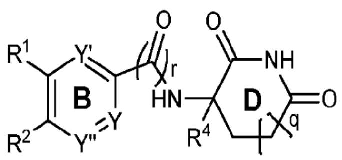
29. The compound of any one of claims 21-28, wherein $R^1$ is hydrogen, halogen, -CN, $-NO_2$, -OH, $-NH_2$, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylamino, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{6-10}$ aryl, 5- to 10-membered heteroaryl, $C_{3-12}$ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more $R^u$.

30. The compound of claim 29, wherein $R^1$ is hydrogen, halogen, or $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

31. The compound of any one of claims 10-30, 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 $R^u$.

32. The compound of claim 31, wherein s is 0.

33. The compound of any one of claims 1-4, wherein **C** is of Formula **I-1-ii**




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

34. The compound of claim 33, wherein $R^2$ is *-$Cy^2$-, wherein * denotes attachment to **L**.

35. The compound of claim 33 or 34, 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 $R^u$.

36. The compound of any one of claims 33-35, 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 $R^u$.

37. The compound of claim 36, wherein $R^1$ is hydrogen, halogen, or $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

38. The compound of any one of claims 33-37, wherein Y is N.

39. The compound of any one of claims 33-37, wherein Y is $CR^Y$, and $R^Y$ is hydrogen, halogen, or $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

40. The compound of any one of claims 33-37, 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 $R^u$.

41. The compound of claim 40, wherein $R^3$ is hydrogen, halogen, or $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

42. The compound of any one of claims 33-41, wherein r is 0.

43. The compound of any one of claims 33-41, wherein r is 1.

44. The compound of any one of claims 1-43, wherein $R^4$ is hydrogen.

45. The compound of any one of claims 1-44, wherein q is 1.

46. The compound of any one of claims 1-45, wherein each of $X^{T1}$, $X^{T2}$, $X^{T3}$, and $X^{T4}$ is $CR^T$.

47. The compound of claim 46, wherein each of $X^{T1}$, $X^{T2}$, $X^{T3}$, and $X^{T4}$ is CH; 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; or one of $X^{T1}$ and $X^{T4}$ is $C(OCH_3)$, the other one of $X^{T1}$ and $X^{T4}$ is CH, and each $X^{T2}$ and $X^{T3}$ is CH.

48. The compound of claim 46, wherein $X^{T1}$ is $C(OCH_3)$, $X^{T3}$ is CF, and each of $X^{T2}$ and $X^{T4}$ is CH; or $X^{T2}$ is CF, $X^{T4}$ is $C(OCH_3)$, and each of $X^{T1}$ and $X^{T3}$ is CH.

49. The compound of any one of claims 1-45, wherein one of $X^{T1}$, $X^{T2}$, $X^{T3}$, and $X^{T4}$ is N.

50. The compound of claim 49, wherein 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 N.

51. The compound of any one of claims 1-45, wherein two of $X^{T1}$, $X^{T2}$, $X^{T3}$, and $X^{T4}$ are N.

52. The compound of claim 51, wherein each of $X^{T1}$ and $X^{T4}$ is CH, and each of $X^{T2}$ and $X^{T3}$ is N.

53. The compound of any one of claims 46-52, 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, 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more $R^u$.

54. The compound of claim 53, wherein each $R^T$ is independently hydrogen, $C_{1-6}$ alkoxy, or halogen.

55. The compound of any one of claims 46-54, 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, $C_{3-12}$ 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 $R^u$.

56. The compound of claim 55, wherein $R^E$ is $C_{1-6}$ alkoxy, wherein the alkoxy is optionally substituted with one or more $R^u$.

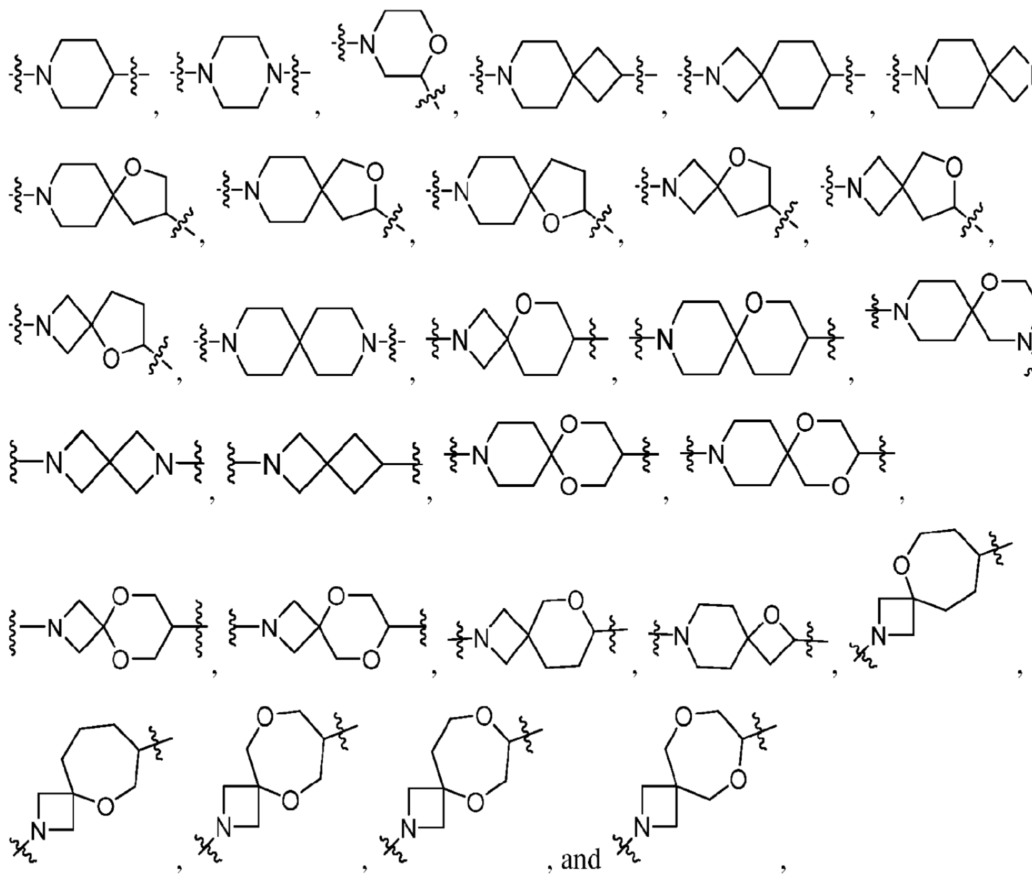
57. The compound of any one of claims 56-56, wherein m is 0.

58. The compound of any one of claims 1-57, 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 $R^u$.

59. The compound of any one of claims 1-57, wherein $Cy^1$ is 3- to 12-membered heterocyclylene, wherein the heterocyclylene is optionally substituted by one or more $R^u$.

60. The compound of claim 59, wherein $Cy^1$ 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 $R^u$.

61. The compound of claim 59, wherein $Cy^1$ is 3- to 12-membered heterocyclylene selected from:



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

62. The compound of any one of claims 58-61, wherein W is absent.

63. The compound of any one of claims 58-62, wherein Z' is absent.

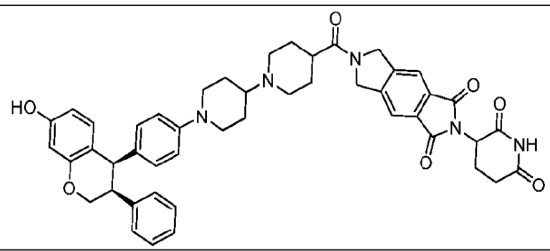
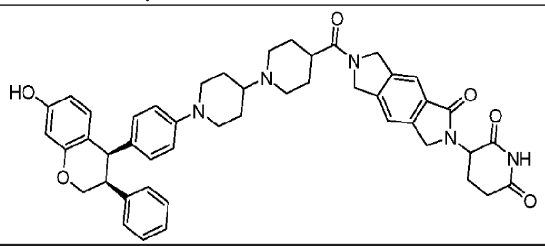
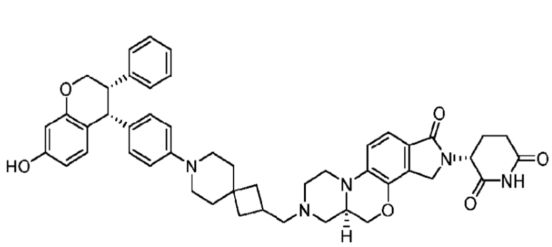
64. The compound of any one of claims 58-62, wherein Z' is -C(=O)-, $C_{1-6}$ alkylene, *-O-($C_{1-6}$ alkylene)-, *-($C_{1-6}$ alkylene)-O-, *-C(=O)-($C_{1-6}$ alkylene)-, *-($C_{1-6}$ alkylene)-C(=O)-, 3- to 12-membered heterocyclylene, *-C(=O)-(3- to 12-membered heterocyclylene)-, *-(3- to 12-membered 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-

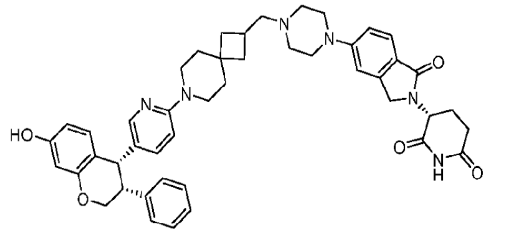
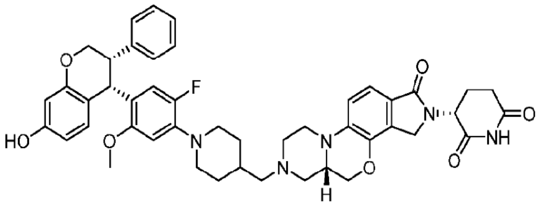
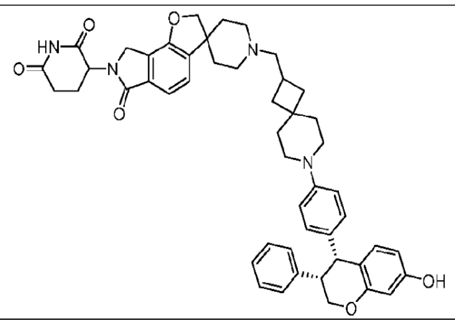
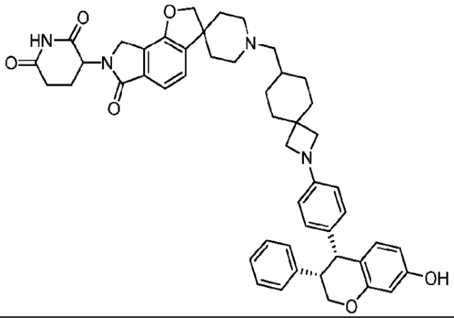
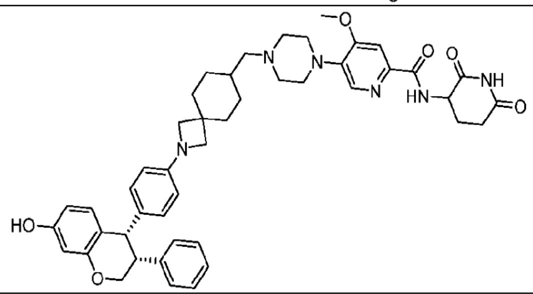
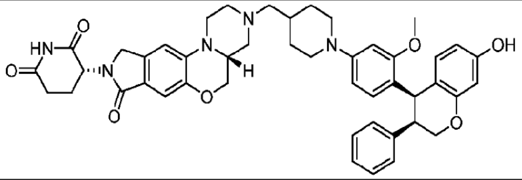
membered heterocyclylene)-(C(=O))-($C_{1-6}$ alkylene)-, wherein the alkylene or heterocyclylene is optionally substituted by one or more $R^u$, and *denotes attachment to **C**.

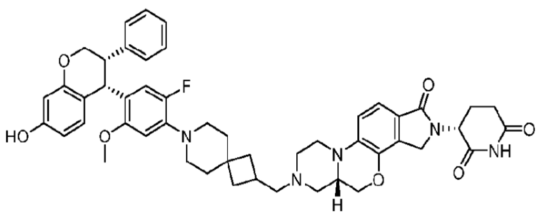
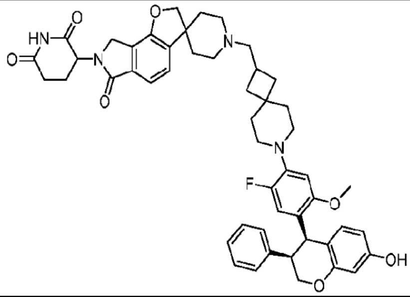
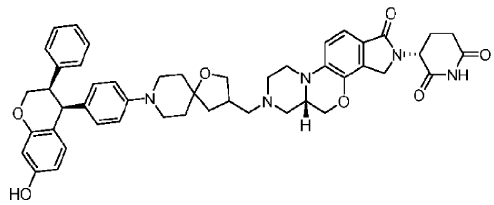
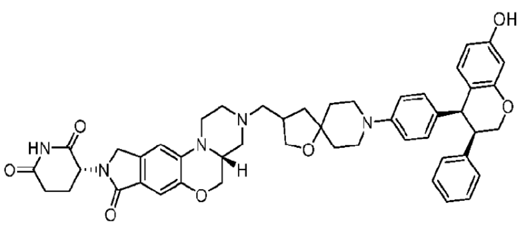
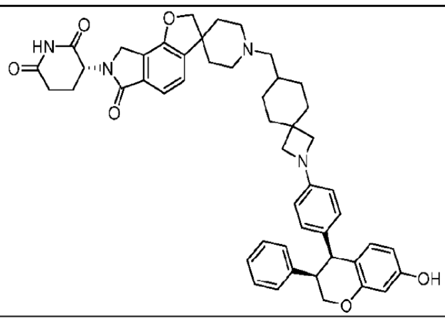
65. The compound of claim 64, wherein Z' is $C_{1-6}$ alkylene, *-C(=O)-($C_{1-6}$ alkylene)-, *-($C_{1-6}$ alkylene)-C(=O)-,*-C(=O)-(3- to 12-membered heterocyclylene)-, or *-(3- to 12-membered heterocyclylene)-($C_{1-6}$ alkylene)-, wherein the alkylene or heterocyclylene is optionally substituted by one or more $R^u$, and *denotes attachment to **C**.

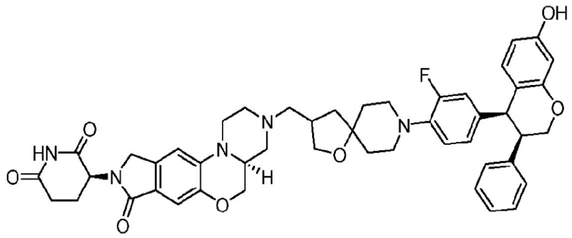
66. A compound selected from the compounds in Tables 1 and 2 or a pharmaceutically acceptable salt thereof.

67. A compound selected from

| Structure | Chemical Name |
|---|---|
|  | 2-(2,6-dioxopiperidin-3-yl)-6-(1'-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione |
|  | 3-(6-(1'-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione |
|  | (R)-3-((R)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |

| | |
|---|---|
|  | (R)-3-(5-(4-((7-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione |
|  | (R)-3-((S)-7-((1-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-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 |
|  | 3-(1'-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
|  | 3-(1'-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-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 |
|  | N-(2,6-dioxopiperidin-3-yl)-5-(4-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide |
|  | (R)-3-((R)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
|  | (R)-3-((S)-7-((7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-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 |
|  | 3-(1'-((7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-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 |
|  | (3R)-3-((5aS)-7-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
|  | (3R)-3-((4aR)-3-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |
|  | (R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |

| | |
|---|---|
|  | (3S)-3-((4aS)-3-((8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-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 |

68. A pharmaceutical composition comprising the compound of any one of claims 1-67, and a pharmaceutically acceptable excipient.

69. A method of degrading an estrogen receptor protein in a patient or biological sample comprising contacting said patient or biological sample with a compound of any one of claims 1-67.

70. Use of a compound of any one of claims 1-67 in the manufacture of a medicament for degrading an estrogen receptor protein in a patient or biological sample.

71. A compound of any one of claims 1-67 for use in degrading an estrogen receptor protein in a patient or biological sample.

72. A method of treating a disease or disorder comprising administering to a patient in need thereof a compound of any one of claims 1-67.

73. Use of a compound of any one of claims 1-67 in the manufacture of a medicament for treating a disease or disorder.

74. A compound of any one of claims 1-67 for use in treating a disease or disorder.

75. The method, use, or compound forr use of any one of claims 72-74, wherein the disease or disorder is an estrogen receptor-mediated disease or disorder.

76. The method, use, or compound forr use of any one of claims 72-74, 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/US2023/027435

**A. CLASSIFICATION OF SUBJECT MATTER**
INV. C07D498/14 C07D498/20 C07D487/04 C07D405/14 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. |
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| E | WO 2023/183607 A1 (UNIV MICHIGAN [US] ET AL.) 28 September 2023 (2023-09-28) claim 1 | 1-76 |
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| X | WO 2021/133886 A1 (ACCUTAR BIOTECHNOLOGY [US]) 1 July 2021 (2021-07-01) | 1-6, 44-66, 68-76 |
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 17 October 2023 | 26/10/2023 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Bérillon, Laurent |

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| International application No |
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C(Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

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| Y | WO 2020/006265 A1 (DANA FARBER CANCER INST INC [US]) 2 January 2020 (2020-01-02) claim 1 ----- | 1-76 |

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Information on patent family members

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