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(54) Title: IKZF2 DEGRADERS AND USES THEREOF

(57) Abstract: Described herein are compounds of Formulae I' and their pharmaceutically acceptable salts, solvates, or stereoisomers, as well as their uses (e.g., as IKZF2 degraders).

IKZF2 DEGRADERS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/446,105, filed February 16, 2023, and U.S. Provisional Application No. 63/323,792, filed March 25, 2022, the contents of each of which are incorporated herein by reference in their entireties.

BACKGROUND

[0002] Described herein IKAROS Family Zinc Finger 2 (IKZF2) (also known as Helios) is one of the five members of the Ikaros family of transcription factors found in mammals. IKZF2 contains four zinc finger domains near the N-terminus, which are involved in DNA binding, and two zinc finger domains at the C-terminus, which are involved in protein dimerization. IKZF2 is about 50% identical with Ikaros family members, Ikaros (IKZF1), Aiolos (IKZF3), and Eos (IKZF4) with highest homology in the zinc finger regions (80%+ identity). These four Ikaros family transcription factors bind to the same DNA consensus site and can heterodimerize with each other when co-expressed in cells. The fifth Ikaros family protein, Pegasus (IKZF5), is only 25% identical to IKZF2, binds a different DNA site than other Ikaros family members and does not readily heterodimerize with the other Ikaros family proteins. IKZF2, IKZFl and IKZF3 are expressed mainly in hematopoietic cells while IKZF4 and IKZF5 are expressed in a wide variety of tissues.

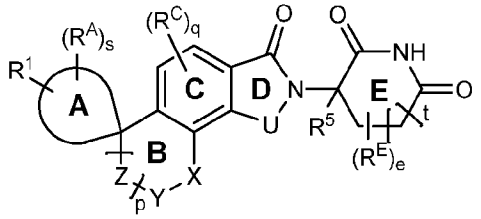
[0003] IKZF2 is a critical regulator of T cell activity and function. Genetic deletion of Helios resulted in an enhanced anti-tumor immune response. Notably, Helios is highly expressed in regulatory T cells, a subpopulation of T cells that restricts the activity of effector T cells. Selective deletion of Helios in regulatory T cells resulted in both loss of suppressive activity and acquisition of effector T cell functions. Therefore, Helios is a critical factor in restricting T cell effector function in Tregs. Currently, anti-CTLA4 antibodies are used in the clinic to target Tregs in tumors. However, targeting CTLA4 often causes systemic activation of T-effector cells, resulting in excessive toxicity and limiting therapeutic utility. Up to 3/4 of patients treated with a combination of anti-PD-l and anti-CTLA4 have reported grade 3 or higher adverse events. Thus, a strong need exists to provide compounds that target Tregs in tumors without causing systemic activation of T-effector cells. An IKZF2-specific degrader has the potential to focus the enhanced immune response to areas within or near tumors

providing a potentially more tolerable and less toxic therapeutic agent for the treatment of cancer.

[0004] Helios expression has also been reported to be upregulated in 'exhausted' T cells, in the settings of both chronic viral infections, as well as in dysfunctional chimeric antigen receptor (CAR) T cells. Overexpression or aberrant expression of Helios and various splice isoforms have been reported in several hematological malignancies, including T cell leukemias and lymphomas. Moreover, knockdown of Helios in a model of mixed lineage leukemia (MLL)-driven myeloid leukemia potently suppressed proliferation and increased cell death. In line with these results, genomic profiling and chromatin accessibility analysis demonstrated that IKZF2 loss led to increased myeloid differentiation. These data suggest that IKZF2 is differentially required in myeloid leukemia cells compared to normal cells. Therefore, depletion of IKZF2 has preferential effect in leukemic stem cells compared to normal hematopoietic stem cells, providing a new strategy for targeting leukemic stem cells.

SUMMARY

[0005] The present disclosure provides compounds of Formula (**I'**):



(I'),

wherein each of the variables in Formula I', 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 further provides methods of degrading an IKZF2 protein in a subject or biological sample comprising administering a compound disclosed herein to the subject or contacting the biological sample with a compound disclosed herein.

[0008] In certain aspects, the present disclosure further provides uses of a compound disclose herein in the manufacture of a medicament for degrading an IKZF2 protein in a subject or biological sample.

[0009] In certain aspects, the present disclosure provides compounds disclosed herein for use in degrading an IKZF2 protein in a subject or biological sample.

[0010] In certain aspects, the present disclosure provides methods of treating a disease or disorder comprising administering to a subject in need thereof a compound disclosed herein.

[0011] 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.

[0012] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating a disease or disorder.

[0013] In certain aspects, the present disclosure provides methods of (a) increasing IL-2 production; (b) suppressing regulatory T cells; (c) enhancing effector T cells; (d) inhibiting tumor growth; and/or (e) enhancing tumor regression in a subject, comprising administering to the subject in need thereof a compound disclosed herein.

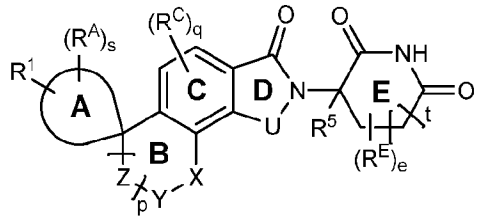
[0014] In certain aspects, the present disclosure provides use of a compound disclosed herein in the manufacture of a medicament for (a) increasing IL-2 production; (b) suppressing regulatory T cells; (c) enhancing effector T cells; (d) inhibiting tumor growth; and/or (e) enhancing tumor regression in a subject.

DETAILED DESCRIPTION

[0015] The present disclosure relates to compounds and methods of degrading a IKZF2 protein comprising contacting a IKZF2 protein with a therapeutically effective amount of a IKZF2 degrader. The invention also relates to methods of treating a IKZF2 protein-mediated disease or condition in a patient by administering a therapeutically effective amount of a IKZF2 degrader to a patient in need thereof. The invention further relates to methods of treating a IKZF2-mediated disease or condition in a patient, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of a IKZF2 degrader to a patient in need thereof.

Compounds of the Present Disclosure

[0016] In certain aspects, the present disclosure provides compounds of Formula (I'):



(I'),

and pharmaceutically acceptable salts, solvates, or stereoisomers thereof, wherein:

X is $-C(R^3)_2-$, $-NR^4-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$;

Y is $-C(R^3)_2-$, $-NR^4-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$;

each Z is independently $-C(R^3)_2-$, $-NR^4-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$;

p is 0, 1, or 2;

each R^3 is independently deuterium, 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, aryl, heteroaryl, carbocyclyl, or heterocyclylis optionally substituted with one or more R^u;

two geminal R^3 together form oxo; or

two geminal R^3, together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl or 3- to 6-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u;

each R^4 is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

Ring A is C_{3-12} carbocycle or 3- to 12-membered heterocycle;

R^1 is hydrogen or $-M-L-Q-R^2$;

M is absent, -(C=O)-, -S(=O)-, or $-S(=O)_2-$;

L is absent or $[W]_r$;

r is an integer from 1 to 3;

each W is independently $-C(R^L)_2-$, C_{3-4} carbocyclylene, or 3- to 4-membered heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted with one or more R^u;

each R^L is independently hydrogen, deuterium, 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; or

two geminal R^L, together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl or 3- to 6-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u;

Q is absent, $-NR^Q-$, -O-, -C(=O)-, -S(=O)-, or $-S(=O)_2-$;

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

R^2 is C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^{2a};

each R^{2a} 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, -(C_{1-6} alkyl)-(C_{6-10} aryl), -(C_{1-6} alkyl)-(5- to 10-membered heteroaryl), -(C_{1-6} alkyl)-(C_{3-12} carbocyclyl), -(C_{1-6} alkyl)-(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, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u; or

two R^{2a}, together with the atoms to which they are bonded, form C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u;

each occurrence of R^A, R^C, and R^E 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;

q is an integer from 0 to 2;

s is an integer from 0 to 12, as valency permits;

e is an integer selected from 0 to 5;

U is $-CH_2-$ or -C(=O)-;

R^5 is hydrogen, deuterium, C_{1-6} haloalkyl, or C_{1-6} alkyl; and

t is an integer from 0 to 2;

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, -(C_{1-6} alkylene)-(C_{6-10} aryl), -(C_{1-6} alkylene)-

(5- to 10-membered heteroaryl), -(C_{1-6} alkylene)-(C_{3-12} carbocyclyl), -(C_{1-6} alkylene)-(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, alkylene, 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_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, and 3- to 12-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

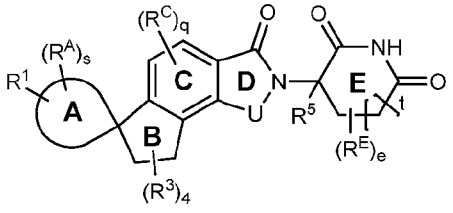
R^c and R^d are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl; or

R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more R^z,

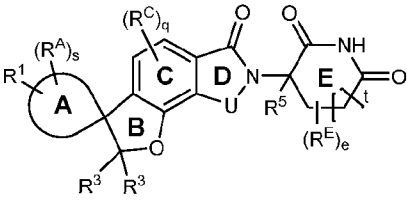
wherein each occurrence of R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z; and

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

[0017] In certain embodiments, the compound is a compound of Formula **(I'-1-i)**, **(I'-1-ii)**, **(I'-1-iii)**, **(I'-1-iv)**, **(I'-1-v)**, **(I'-1-vi)**, **(I'-1-vii)**, **(I'-1-viii)**, **(I'-1-ix)**, **(I'-1-x)**, **(I'-1-xi)**, **(I'-1-xii)**, or **(I'-1-xiii)**:



(I'-1-i),



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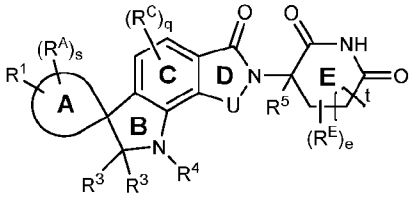
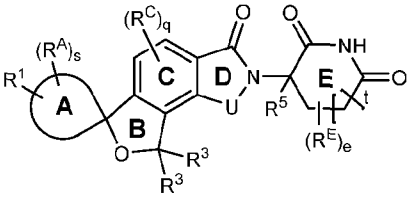
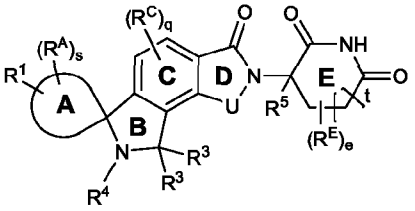


(I'-1-iii),



(I'-1-iv),



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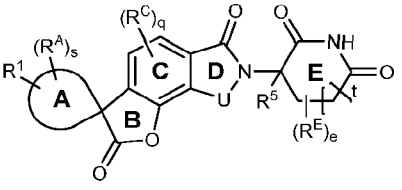
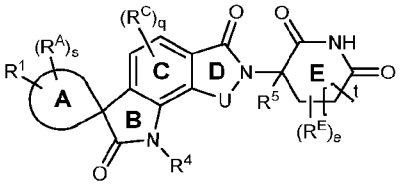
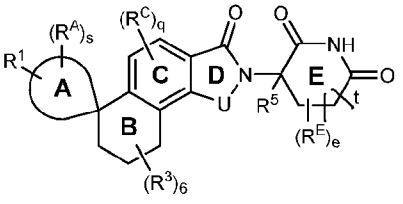


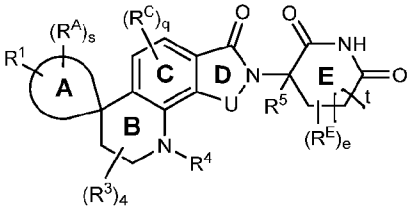
(I'-1-vi),



(I'-1-vii),



(I'-1-viii),



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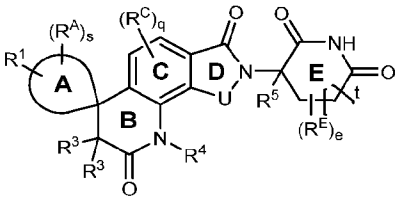
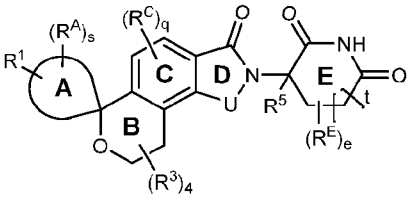
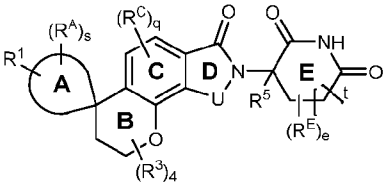


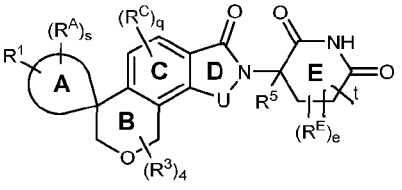
(I'-1-x),



(I'-1-xi),



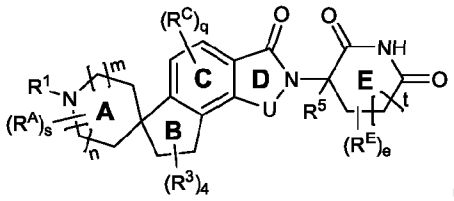
(I'-1-xii), or



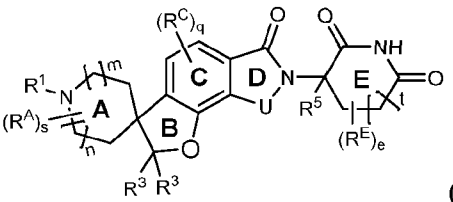
(I'-1-xiii),

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

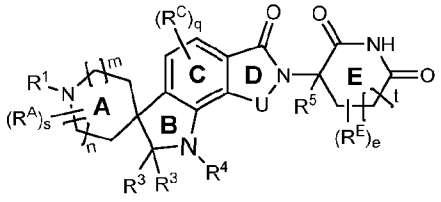
[0018] In certain embodiments, the compound is a compound of Formula **(I'-2-i)**, **(I'-2-ii)**, **(I'-2-iii)**, **(I'-2-iv)**, **(I'-2-v)**, **(I'-2-vi)**, **(I'-2-vii)**, **(I'-2-viii)**, **(I'-2-ix)**, **(I'-2-x)**, **(I'-2-xi)**, **(I'-2-xii)**, or **(I'-2-xiii)**:



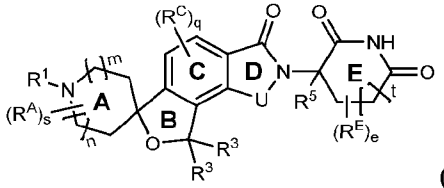
(I'-2-i),



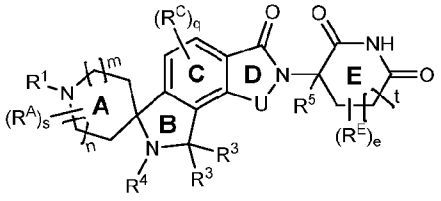
(I'-2-ii),



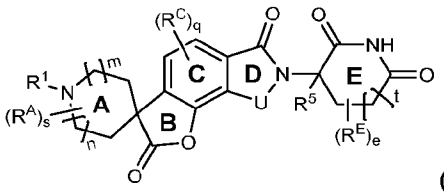
(I'-2-iii),



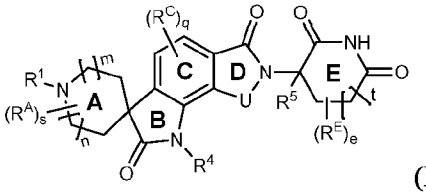
(I'-2-iv),



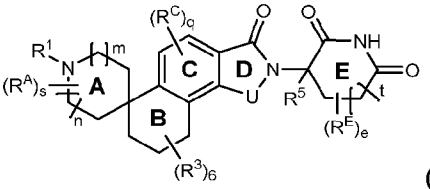
(I'-2-v),



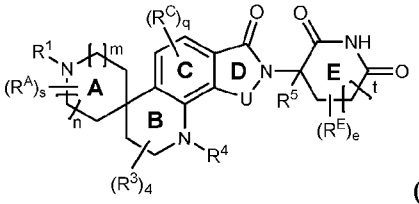
(I'-2-vi),



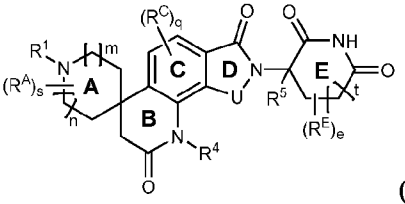
(I'-2-vii),



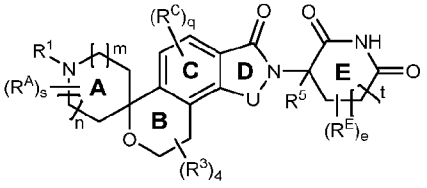
(I'-2-viii),



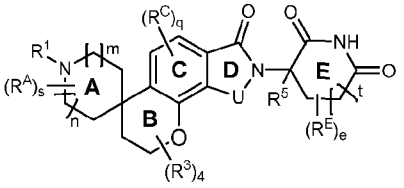
(I'-2-ix),



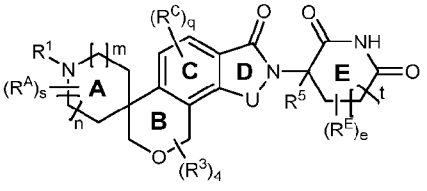
(I'-2-x),



(I'-2-xi),



(I'-2-xii), or

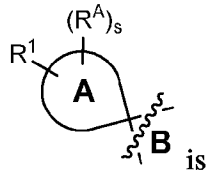
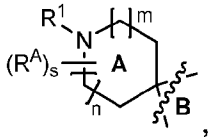


(I'-2-xiii),

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[0019] In certain embodiments, when p is 0, then X and Y are not both $-C(R^3)_2$; and/or when p is 1, then X, Y, and Z are not all $-C(R^3)_2$.

[0020] In certain embodiments, Ring A is C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})) or 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S).

[0021] In certain embodiments,  is  , wherein m and n are independently an integer from 0 to 2.

[0022] In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2.

[0023] In certain embodiments, each of m and n is 1.

[0024] In certain embodiments, R^1 is hydrogen or $-M-L-Q-R^2$.

[0025] In certain embodiments, M is absent, -(C=O)-, -S(=O)-, or $-S(=O)_2-$.

[0026] In certain embodiments, L is absent or $[W]_r$.

[0027] In certain embodiments, each W is independently $-C(R^L)_2-$, C_{3-4} carbocyclylene (*e.g.*, cyclopropylene (C_3), cyclopropenylene (C_3), cyclobutylene (C_4), or cyclobutenylene (C_4)), or 3- to 4-membered heterocyclylene (*e.g.*, heterocyclylene comprising one 3- to 4-membered rings and 1 heteroatom selected from N, O, and S), wherein the carbocyclylene or heterocyclylene is optionally substituted with one or more R^u.

[0028] In certain embodiments, each R^L is independently hydrogen, deuterium, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0029] In certain embodiments, each R^L is independently hydrogen, deuterium, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0030] In certain embodiments, each R^L is independently hydrogen, deuterium, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0031] In certain embodiments, each R^L is independently hydrogen, deuterium, 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.

[0032] In certain embodiments, each R^L is independently hydrogen, deuterium, or C_{1-6} alkyl.

[0033] In certain embodiments, L is $-CH_2-$.

[0034] In certain embodiments, two geminal R^L, together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), or cyclohexadienyl (C_6)) or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 6-membered rings and 1-3 heteroatoms selected from N, O, and S), wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

[0035] In certain embodiments, r is an integer from 1 to 3. In certain embodiments, r is 1. In certain embodiments, r is 1. In certain embodiments, r is 2. In certain embodiments, r is 3.

[0036] In certain embodiments, Q is absent, $-NR^Q-$, -O-, -C(=O)-, -S(=O)-, or $-S(=O)_2-$.

[0037] In certain embodiments, R^Q is hydrogen or C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)) optionally substituted with one or more R^u.

[0038] In certain embodiments, R^2 is C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and

S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^{2a}.

[0039] In certain embodiments, each R^{2a} is independently oxo, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -(C_{1-6} alkylene)-(C_{6-10} aryl), -(C_{1-6} alkylene)-(5- to 10-membered heteroaryl), -(C_{1-6} alkylene)-(C_{3-12} carbocyclyl), -(C_{1-6} alkylene)-(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, alkylene, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0040] In certain embodiments, each R^{2a} is independently oxo, halogen, -CN, -OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkylamino, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -(C_{1-6} alkylene)-(C_{6-10} aryl), -(C_{1-6} alkylene)-(5- to 10-membered heteroaryl), -(C_{1-6} alkylene)-(C_{3-12} carbocyclyl), -(C_{1-6} alkylene)-(3- to 12-membered heterocyclyl), $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^bC(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkylene, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0041] In certain embodiments, two R^{2a}, together with the atoms to which they are bonded, form C_{3-8} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8)) or 3- to 8-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-3 heteroatoms selected from N, O, and S) , wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

[0042] In certain embodiments, each occurrence of R^A, R^C, and R^E is independently oxo, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-

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

[0043] In certain embodiments, each occurrence of R^A, R^C, and R^E is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0044] In certain embodiments, each occurrence of R^A, R^C, and R^E is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0045] In certain embodiments, each occurrence of R^A, R^C, and R^E is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0046] In certain embodiments, q is an integer from 0 to 2. In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2.

[0047] In certain embodiments, s is an integer from 0 to 12, as valency permits. 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, as valency permits. In certain embodiments, s is 6, as valency permits. In certain embodiments, s is 7, as valency permits. In certain embodiments, s is 8, as valency permits. In certain embodiments, s is 9, as valency permits. In certain embodiments, s is 10, as valency permits. In certain embodiments, s is 11, as valency permits. In certain embodiments, s is 12, as valency permits.

[0048] In certain embodiments, e is an integer selected from 0 to 5. In certain embodiments, e is 0. In certain embodiments, e is 1. In certain embodiments, e is 2. In certain embodiments, e is 3. In certain embodiments, e is 4. In certain embodiments, e is 5.

[0049] In certain embodiments, X is $-C(R^3)_2-$, $-NR^4-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$.

[0050] In certain embodiments, Y is $-C(R^3)_2-$, $-NR^4-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$.

[0051] In certain embodiments, each Z is independently $-C(R^3)_2-$, $-NR^4-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$.

[0052] In certain embodiments, X is -O- and Y is $-C(R^3)_2-$. In certain embodiments, X is $-C(R^3)_2-$ and Y is -O-. In certain embodiments, X is $-NR^4-$ and Y is $-C(R^3)_2-$.

[0053] In certain embodiments, p is 0, 1, or 2. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2.

[0054] In certain embodiments, each R^3 is independently deuterium, hydrogen, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-

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

[0055] In certain embodiments, each R^3 is independently hydrogen, deuterium, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0056] In certain embodiments, each R^3 is independently hydrogen, deuterium, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0057] In certain embodiments, each R^3 is independently hydrogen, deuterium, 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.

[0058] In certain embodiments, each R^3 is independently hydrogen, deuterium, or C_{1-6} alkyl.

[0059] In certain embodiments, two geminal R^3 together form oxo.

[0060] In certain embodiments, two geminal R^3, together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), or cyclohexadienyl (C_6)) or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 6-membered rings and 1-3 heteroatoms selected from N, O, and S), wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

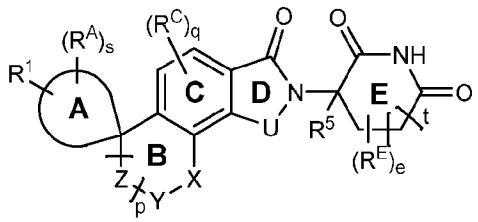
[0061] In certain embodiments, each R^4 is independently hydrogen or C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)) optionally substituted with one or more R^u.

[0062] In certain embodiments, U is $-CH_2-$ or -C(=O)-.

[0063] In certain embodiments, R^5 is hydrogen, deuterium, C_{1-6} haloalkyl (*e.g.*, C_{1-6} alkyl substituted by 1 to 8 halogen atoms selected from -F, -Cl, -Br, or -I), or C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)).

[0064] In certain embodiments, t is an integer from 0 to 2. In certain embodiments, t is 0. In certain embodiments, t is 1. In certain embodiments, t is 2.

[0065] In certain embodiments, the compound is a compound of Formula (I'):



(I'),

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^1 is hydrogen or $-L-R^2$;

L is $-C(R^L)_2-$;

each R^L is independently hydrogen, deuterium, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

R^2 is C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^{2a};

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

each occurrence of R^A, R^C, and R^E is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

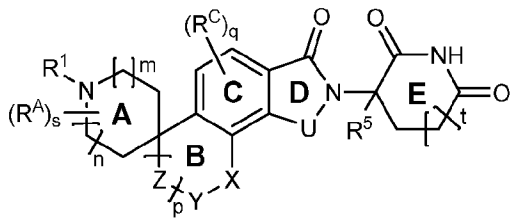
X is -O- or -NR^4-;

each R^4 is independently hydrogen or C_{1-6} alkyl;

Y is -CH_2- or -O-; and

p is 0 or 1.

[0066] In certain aspects, the present disclosure provides compounds of Formula (I):



(I),

and pharmaceutically acceptable salts, solvates, or stereoisomers thereof, wherein:

R^1 is hydrogen or -M-L-Q-R^2;

M is absent, -(C=O)-, -S(=O)-, or -$S(=O)_2$-;

L is absent or [-$C(R^L)_2$-]$_r$;

each R^L 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, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; or

two R^L, together with the carbon atom(s) to which they are attached, form C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl;

r is an integer from 1 to 3;

Q is absent, $-NR^Q-$, -O-, -C(=O)-, -S(=O)-, or $-S(=O)_2-$;

R^Q is hydrogen, C_{1-6} alkyl, wherein the alkyl is optionally substituted with one or more R^u;

R^2 is C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^{2a};

each R^{2a} 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, -(C_{1-6} alkyl)-(C_{6-10} aryl), -(C_{1-6} alkyl)-(5- to 10-membered heteroaryl), -(C_{1-6} alkyl)-(C_{3-12} carbocyclyl), -(C_{1-6} alkyl)-(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

two R^{2a} together form oxo;

each occurrence of R^A and R^C 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;

q is an integer from 0 to 2;

s is an integer from 0 to 12, as valency permits;

m and n are independently an integer from 0 to 2;

X is $-C(R^3)_2-$, $-NR^4-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$;

Y is $-C(R^3)_2-$, $-NR^4-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$;

each Z is independently $-C(R^3)_2-$, $-NR^4-$, -O-, -S-, -S(=O)-, or $-S(=O)_2-$;

p is 0 or 1;

each R^3 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^3 together form oxo; or

two R^3, together with the carbon atom(s) to which they are attached, form C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl;

each R^4 is independently hydrogen or C_{1-6} alkyl, wherein the alkyl is optionally substituted with one or more R^u;

U is $-CH_2-$ or -C(=O)-;

R^5 is hydrogen, deuterium, C_{1-6} haloalkyl, or C_{1-6} alkyl; and

t is an integer from 0 to 2;

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, $-(C_{1-6}$ alkyl)-(C_{6-10} aryl), $-(C_{1-6}$ alkyl)-(5- to 10-membered heteroaryl), $-(C_{1-6}$ alkyl)-(C_{3-12} carbocyclyl), $-(C_{1-6}$ alkyl)-(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_{3-12} carbocyclyl, and 3- to 6-membered heterocyclyl; or

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

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

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

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

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

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

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

[0067] In certain embodiments, X is $-C(R^3)_2-$.

[0068] In certain embodiments, X is $-NR^4-$.

[0069] In certain embodiments, X is -O-.

[0070] In certain embodiments, X is -S-.

[0071] In certain embodiments, X is -S(=O)-.

[0072] In certain embodiments, X is $-S(=O)_2-$.

[0073] In certain embodiments, Y is $-C(R^3)_2-$.

[0074] In certain embodiments, Y is $-NR^4-$.

[0075] In certain embodiments, Y is -O-.

[0076] In certain embodiments, Y is -S-.

[0077] In certain embodiments, Y is -S(=O)-.

[0078] In certain embodiments, Y is $-S(=O)_2-$.

[0079] In certain embodiments, X is -O- and Y is $-C(R^3)_2-$. In some embodiments, X is -O-, and Y is $-CH_2-$. In certain embodiments, X is $-C(R^3)_2-$ and Y is -O-. In certain embodiments, X is $-NR^4-$ and Y is $-C(R^3)_2-$. In certain embodiments, X is $-C(R^3)_2-$ and Y is $-NR^4-$.

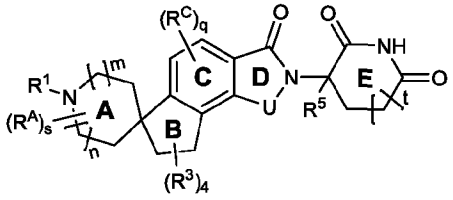
[0080] In some embodiments, X is -O-, Y is $-C(R^3)_2-$, and p is 0.

[0081] In certain embodiments, Z is $-C(R^3)_2-$, $-NR^4-$, or -O-. In certain embodiments, Z is $-C(R^3)_2$ or -O-.

[0082] In certain embodiments, when p is 0, then X and Y are not both $-C(R^3)_2$; or when p is 1, then X, Y, and Z are not all $-C(R^3)_2$.

[0083] In certain embodiments, p is 0. In certain embodiments, p is 1.

[0084] In certain embodiments, the compound is a compound of Formula **(I-1-i)** to **(I-1-xiii)**:



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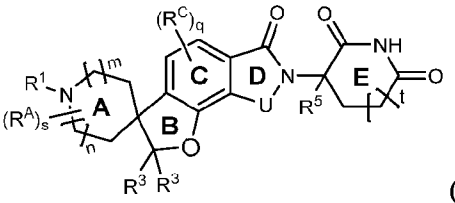

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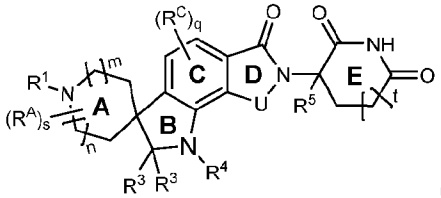

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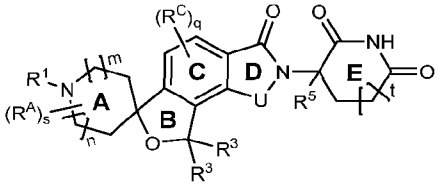

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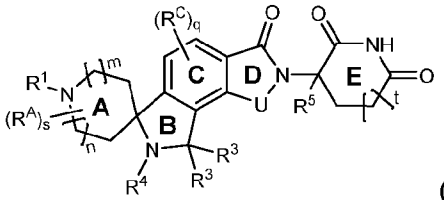

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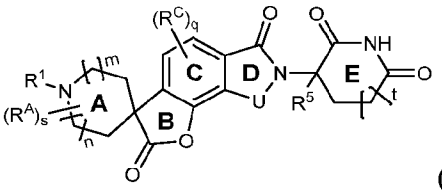

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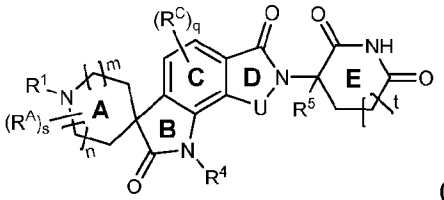

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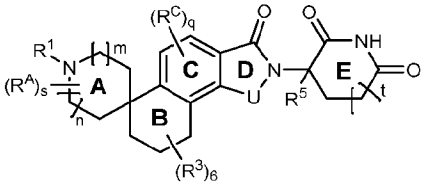

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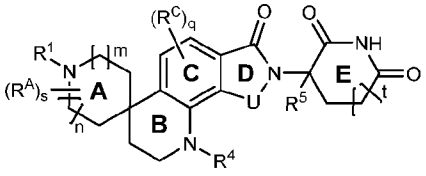

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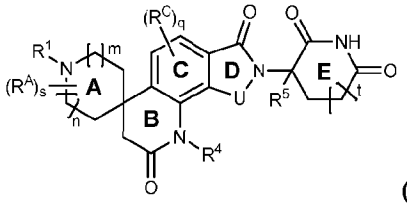

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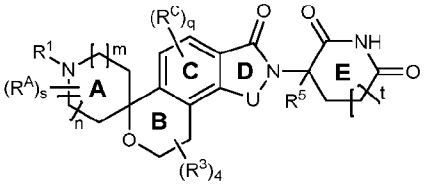

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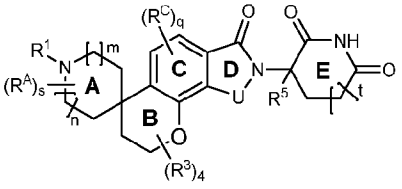
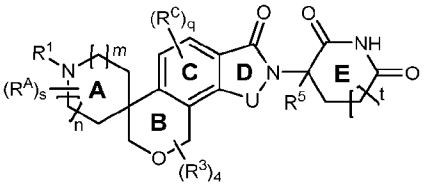


(I-1-xii), or



(I-1-xiii),

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[0085] In certain embodiments, R^1 is hydrogen. In certain embodiments, R^1 is -M-L-Q-R^2.

[0086] In certain embodiments, M is absent. In certain embodiments, M is -(C=O)-, -S(=O)-, or -$S(=O)_2$-.

[0087] In certain embodiments, L is -$C(R^L)_2$-. In certain embodiments, L is absent.

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

[0089] In certain embodiments, each R^L is independently hydrogen or C_{1-6} alkyl.

[0090] In certain embodiments, L is -CH_2-.

[0091] In certain embodiments, two R^L, together with the carbon atom(s) to which they are attached, form C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl.

[0092] In certain embodiments, Q is absent. In certain embodiments, Q is -NR^Q-, -O-, -C(=O)-, -S(=O)-, or -$S(=O)_2$-. In certain embodiments, Q is -NR^Q-. In certain embodiments, Q is -O-. In certain embodiments, Q is -C(=O)-. In certain embodiments, Q is -S(=O)-. In certain embodiments, Q is -$S(=O)_2$-.

[0093] In certain embodiments, R^Q is hydrogen or C_{1-6} alkyl. In certain embodiments, R^Q is C_{1-6} alkyl. In certain embodiments, R^Q is hydrogen.

[0094] In certain embodiments, R^2 is C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{5-10} carbocyclyl, or 5- to 10-membered heterocyclyl.

[0095] In certain embodiments, R^2 is phenyl.

[0096] In certain embodiments, R^2 is 5- to 10-membered heteroaryl.

[0097] In certain embodiments, R^2 is C_{5-10} carbocyclyl.

[0098] In certain embodiments, R^2 is 5- to 10-membered heterocyclyl.

[0099] In certain embodiments, each R^{2a} is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0100] In certain embodiments, each R^{2a} is independently oxo, halogen, -CN, -OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -$S(=O)_2R^a$, -$S(=O)_2NR^cR^d$, -$NR^cS(=O)_2R^a$, -$NR^bC(=O)R^a$, -$C(=O)OR^b$, 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.

[0101] In certain embodiments, two R^{2a} together form oxo.

[0102] In certain embodiments, each R^3 is independently H or C_{1-6} alkyl. In certain embodiments, each R^3 is H. In certain embodiments, two geminal R^3 together form oxo.

[0103] In certain embodiments, each R^4 is independently hydrogen, C_{1-6} alkyl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u. In certain embodiments, each R^4 is independently H or C_{1-6} alkyl, wherein the alkyl is optionally substituted with one or more R^u.

[0104] In certain embodiments, each occurrence of R^A and R^C is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0105] 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. In certain embodiments, s is 9. In certain embodiments, s is 10. In certain embodiments, s is 11. In certain embodiments, s is 12.

[0106] In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2.

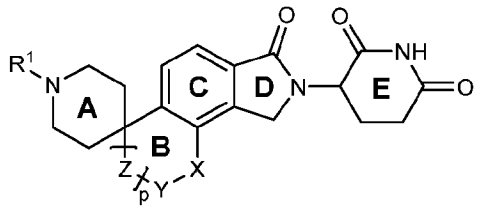
[0107] In certain embodiments, m and n are independently 0 or 1. In certain embodiments, each of m and n is 0. In certain embodiments, each of m and n is 1. In certain embodiments, m is 0 and n is 1. In certain embodiments, m is 1 and n is 0.

[0108] In certain embodiments, U is $-CH_2-$. In certain embodiments, U is -C(=O)-.

[0109] In certain embodiments, R^5 is hydrogen, deuterium, C_{1-6} haloalkyl, or C_{1-6} alkyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is deuterium. In certain embodiments, R^5 is C_{1-6} haloalkyl. In certain embodiments, R^5 is C_{1-6} alkyl.

[0110] In certain embodiments, t is 0. In certain embodiments, t is 1. In certain embodiments, t is 2.

[0111] In certain embodiments, the compound is a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^1 is hydrogen or -L-R^2;

L is -CH_2-;

R^2 is C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^{2a};

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

X is -O-;

Y is -CH_2-; and

p is 0.

[0112] In certain embodiments, each R^a is independently C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0113] In certain embodiments, each R^a is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl.

[0114] In certain embodiments, each R^a is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl.

[0115] In certain embodiments, each R^a is independently C_{1-6} alkyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0116] In certain embodiments, each R^b is independently hydrogen, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0117] In certain embodiments, each R^b is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl.

[0118] In certain embodiments, each R^b is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl.

[0119] In certain embodiments, each R^b is independently hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, or C_{2-6} alkynyl, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0120] In certain embodiments, each R^c and each R^d is independently hydrogen, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3),

cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0121] In certain embodiments, each R^c and each R^d is independently hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, carbocyclyl, or heterocyclylis optionally substituted with one or more R^u.

[0122] In certain embodiments, R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the heterocyclyl is optionally substituted with one or more R^z.

[0123] In certain embodiments, R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z.

[0124] In certain embodiments, R^z is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl.

[0125] In certain embodiments, each R^u is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-

butylamino, propyl-*t*-butylamino, propylpentylylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (*e.g.*, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl (C_{10}), or spiro[4.5]decanyl (C_{10})), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl.

[0126] In certain embodiments, each R^u is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl.

[0127] In certain embodiments, each R^u is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally

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

[0128] In certain embodiments, each R^u is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl or heterocyclyl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl.

[0129] In certain embodiments, each R^u is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl or heterocyclyl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, and 3- to 6-membered heterocyclyl.

[0130] In certain embodiments, two R^u, together with the carbon atom(s) to which they are attached, form C_{3-6} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), or cyclohexadienyl (C_6)) or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms selected from N, O, and S).

[0131] In certain embodiments, two geminal R^u, together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), or cyclohexadienyl (C_6)) or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms selected from N, O, and S).

[0132] Embodiments of the variables in any of the Formulae described herein, *e.g.*, Formulae **I** and **I'**, as applicable, are described below. Any of the variables can be any moiety as described in the embodiments below. In addition, the combination of any moieties described for any of the variables, as applicable, with any moieties described for any of the remaining variables, is also contemplated.

[0133] Without wishing to be limited by this statement, while various options for variables are described herein, it is understood that the present disclosure intends to encompass operable embodiments having combinations of the options. The disclosure may be interpreted as excluding the non-operable embodiments caused by certain combinations of the options. For

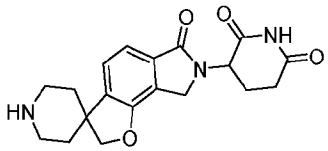
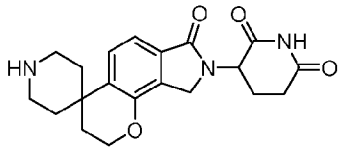
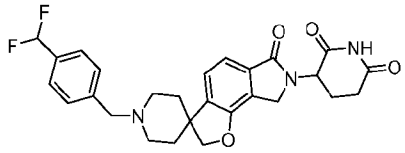
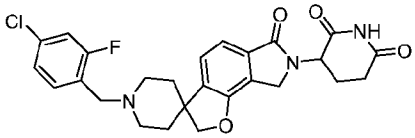
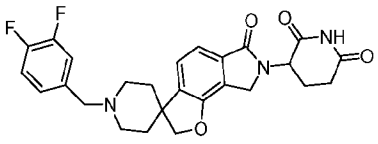
example, while various options for variables X, Y, and Z are described herein, the disclosure may be interpreted as excluding structures for non-operable compounds caused by certain combinations of the options (e.g., when two adjacent members of X, Y, an Z are both nitrogen or both oxygen; or one of two adjacent members of X, Y, and Z is nitrogen while the other is oxygen).

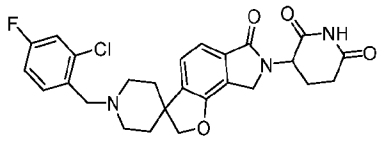
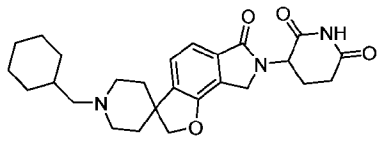
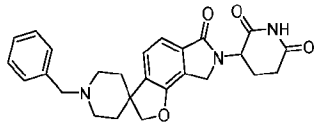
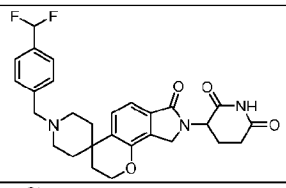
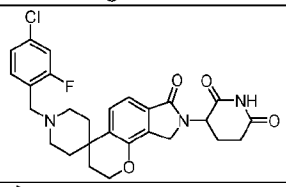
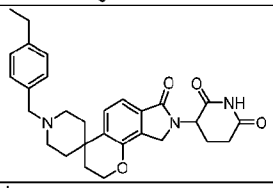
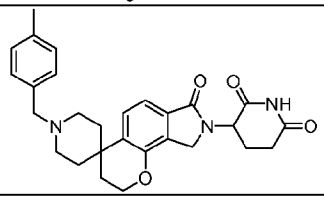
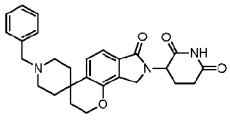
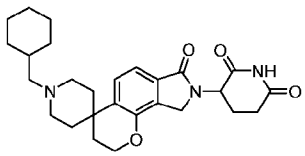
[0134] When a range of values is listed, each discrete value and sub-range within the range are also contemplated. For example, "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

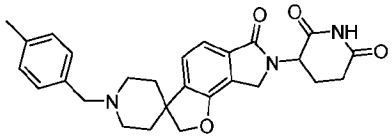
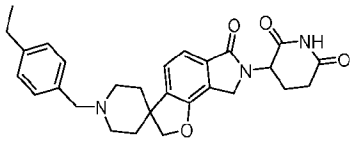
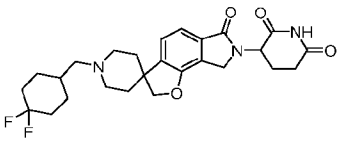
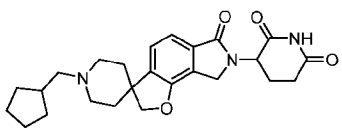
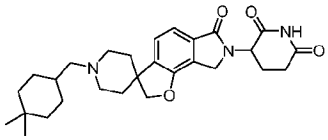
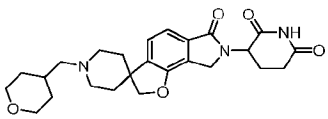
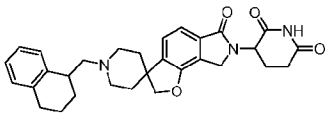
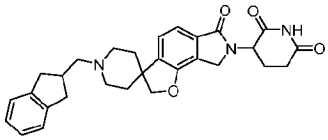
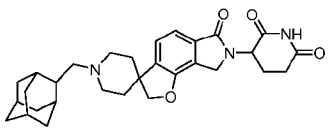
[0135] In certain embodiments, the compound is selected from the compounds in Table 1 and pharmaceutically acceptable salts thereof.

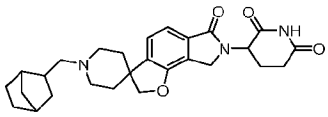
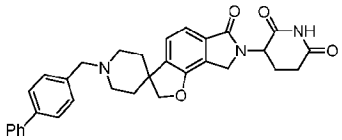
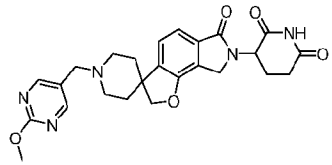
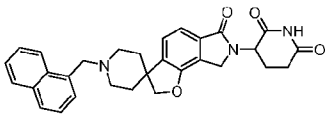
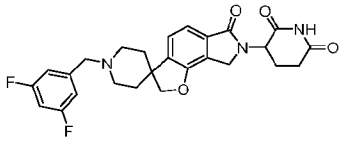
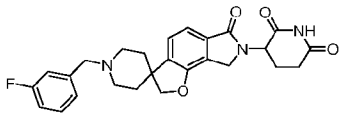
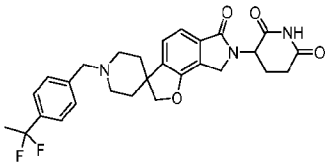
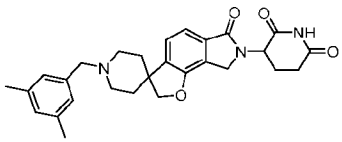
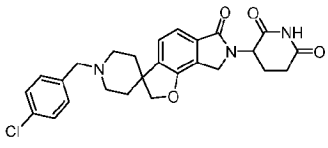
[0136] In certain embodiments, the compound is selected from the compounds in Table 1.

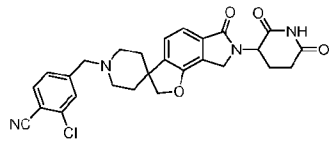
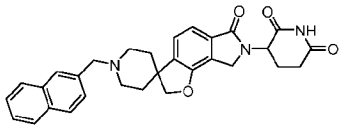
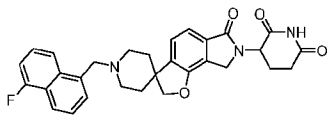
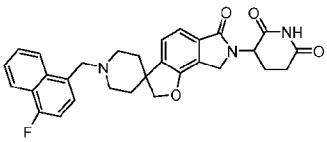
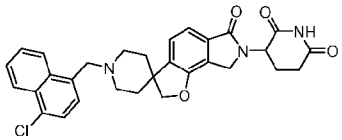
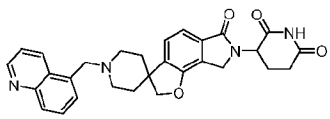
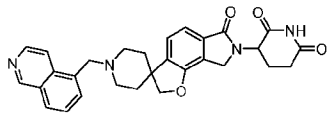
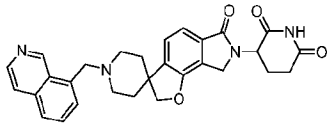
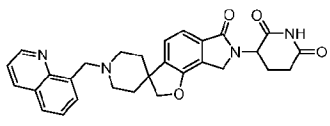
Table 1.

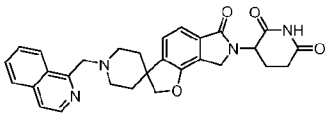
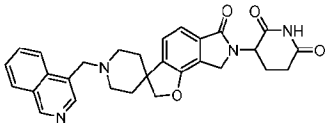
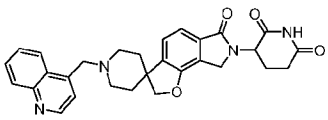
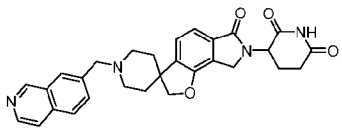
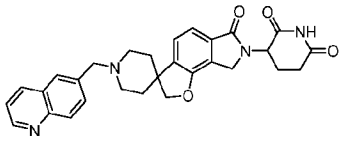
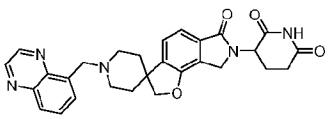
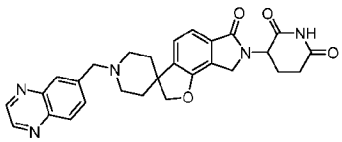
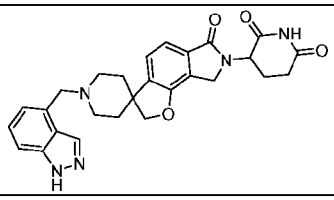
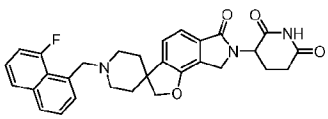
No.	Structure	Compound Name
A1		3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A2		3-(7'-oxo-2',3',7',9'-tetrahydro-8'H-spiro[piperidine-4,4'-pyrano[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
A3		3-(1'-(4-(difluoromethyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A4		3-(1'-(4-chloro-2-fluorobenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A5		3-(1'-(3,4-difluorobenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

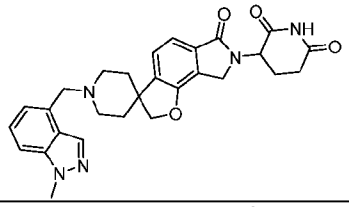
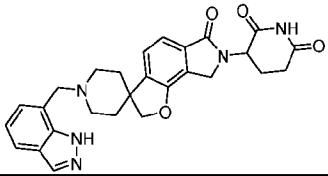
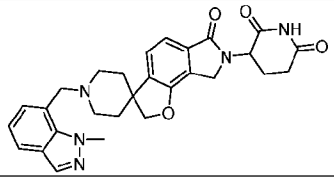
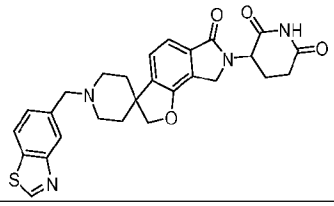
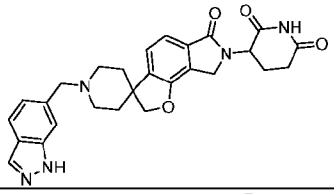
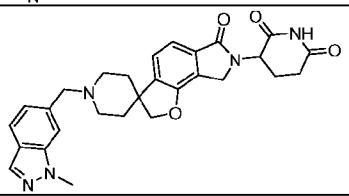
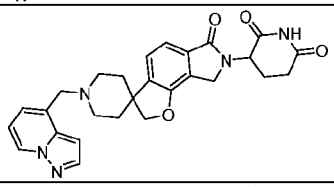
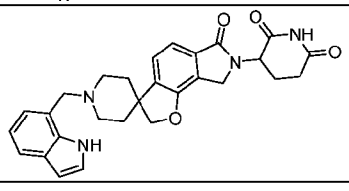
No.	Structure	Compound Name
A6		3-(1'-(2-chloro-4-fluorobenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A7		3-(1'-(cyclohexylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A8		3-(1'-benzyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A9		3-(1-(4-(difluoromethyl)benzyl)-7'-oxo-2',3',7',9'-tetrahydro-8'H-spiro[piperidine-4,4'-pyrano[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
A10		3-(1-(4-chloro-2-fluorobenzyl)-7'-oxo-2',3',7',9'-tetrahydro-8'H-spiro[piperidine-4,4'-pyrano[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
A11		3-(1-(4-ethylbenzyl)-7'-oxo-2',3',7',9'-tetrahydro-8'H-spiro[piperidine-4,4'-pyrano[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
A12		3-(1-(4-methylbenzyl)-7'-oxo-2',3',7',9'-tetrahydro-8'H-spiro[piperidine-4,4'-pyrano[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
A13		3-(1-benzyl-7'-oxo-2',3',7',9'-tetrahydro-8'H-spiro[piperidine-4,4'-pyrano[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione
A14		3-(1-(cyclohexylmethyl)-7'-oxo-2',3',7',9'-tetrahydro-8'H-spiro[piperidine-4,4'-pyrano[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione

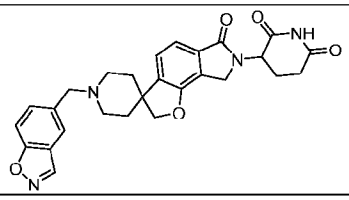
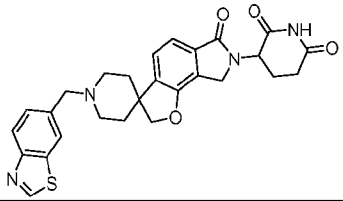
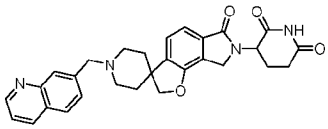
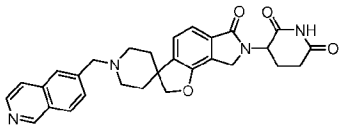
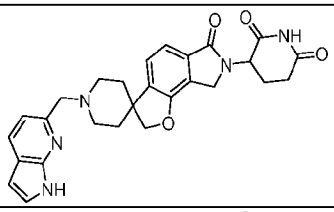
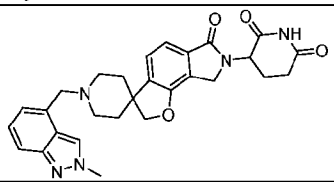
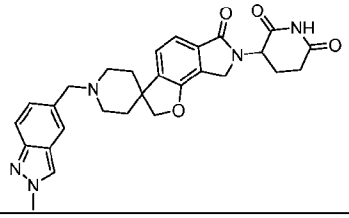
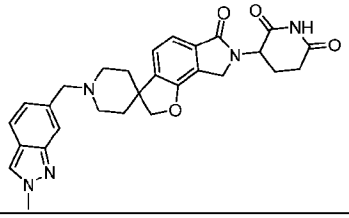
No.	Structure	Compound Name
A15		3-(1'-(4-methylbenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A16		3-(1'-(4-ethylbenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A17		3-(1'-((4,4-difluorocyclohexyl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A18		3-(1'-(cyclopentylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A19		3-(1'-((4,4-dimethylcyclohexyl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A20		3-(6-oxo-1'-((tetrahydro-2H-pyran-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A21		3-(6-oxo-1'-((1,2,3,4-tetrahydronaphthalen-1-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A22		3-(1'-((2,3-dihydro-1H-inden-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
A23		3-(1'-(((1r,3r,5r,7r)-adamantan-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

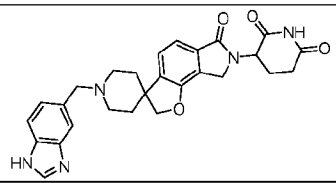
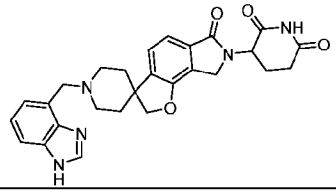
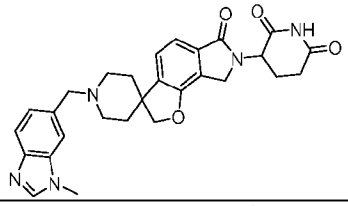
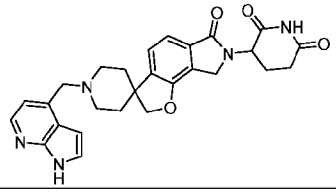
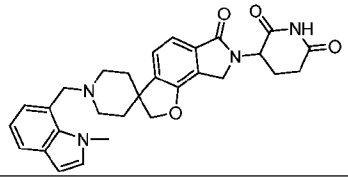
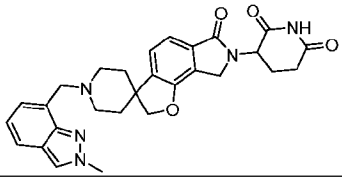
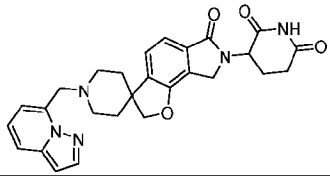
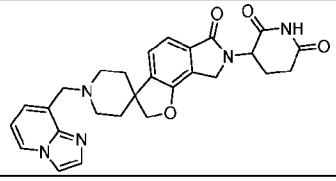
No.	Structure	Compound Name
A24		3-(1'-(bicyclo[2.2.1]heptan-2-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A25		3-(1'-([1,1'-biphenyl]-4-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A26		3-(1'-((2-methoxypyrimidin-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A27		3-(1'-(naphthalen-1-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A28		3-(1'-(3,5-difluorobenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A29		3-(1'-(3-fluorobenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A30		3-(1'-(4-(1,1-difluoroethyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A31		3-(1'-(3,5-dimethylbenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A32		3-(1'-(4-chlorobenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

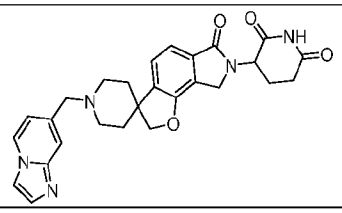
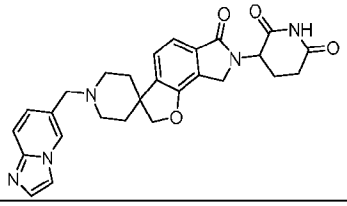
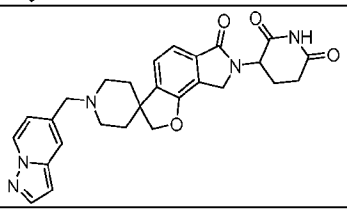
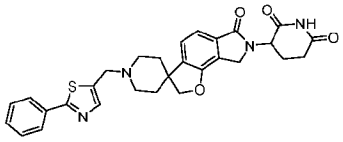
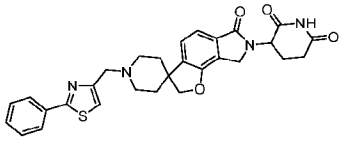
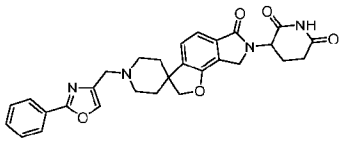
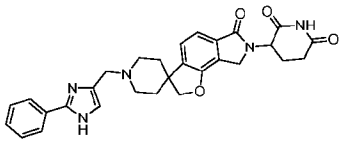
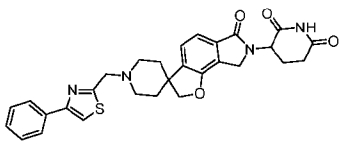
No.	Structure	Compound Name
A33		2-chloro-4-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)benzonitrile
A34		3-(1'-(naphthalen-2-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A35		3-(1'-((5-fluoronaphthalen-1-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A36		3-(1'-((4-fluoronaphthalen-1-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A37		3-(1'-((4-chloronaphthalen-1-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A38		3-(6-oxo-1'-(quinolin-5-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A39		3-(1'-(isoquinolin-5-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A40		3-(1'-(isoquinolin-8-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A41		3-(6-oxo-1'-(quinolin-8-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

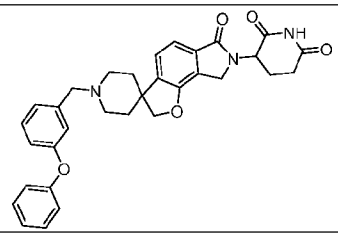
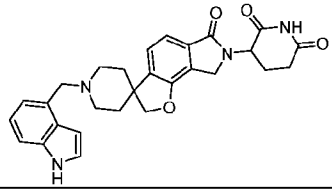
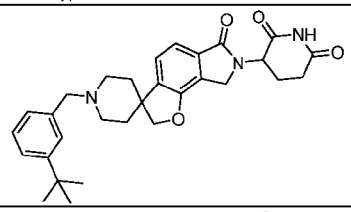
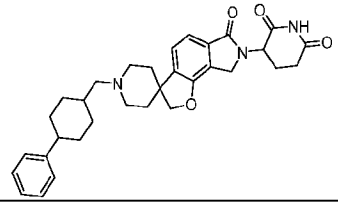
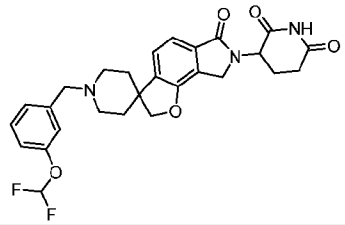
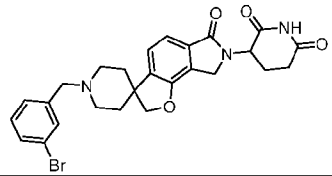
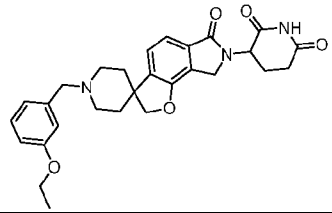
No.	Structure	Compound Name
A42		3-(1'-(isoquinolin-1-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A43		3-(1'-(isoquinolin-4-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A44		3-(6-oxo-1'-(quinolin-4-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A45		3-(1'-(isoquinolin-7-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A46		3-(6-oxo-1'-(quinolin-6-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A47		3-(6-oxo-1'-(quinoxalin-5-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A48		3-(6-oxo-1'-(quinoxalin-6-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A49		3-(1'-((1H-indazol-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
A50		3-(1'-((8-fluoronaphthalen-1-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

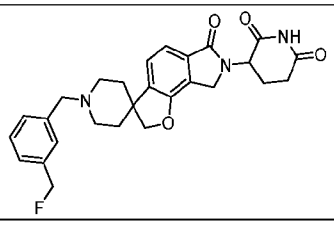
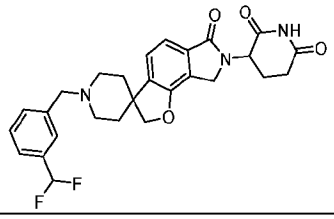
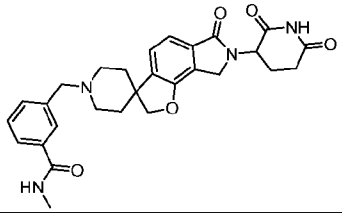
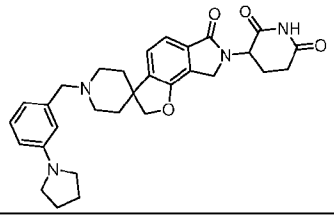
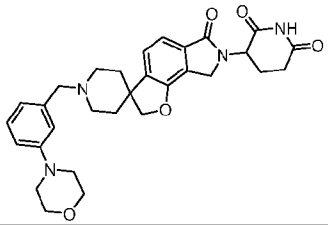
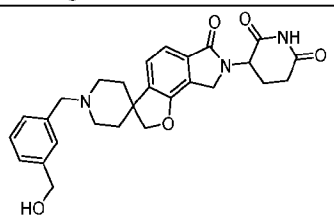
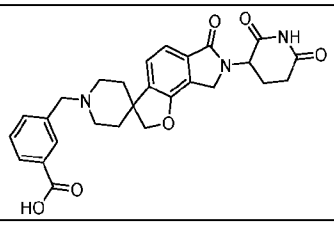
No.	Structure	Compound Name
A51		3-(1'-((1-methyl-1H-indazol-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A52		3-(1'-((1H-indazol-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A53		3-(1'-((1-methyl-1H-indazol-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
A54		3-(1'-(benzo[d]thiazol-5-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A56		3-(1'-((1H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A57		3-(1'-((1-methyl-1H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A58		3-(6-oxo-1'-(pyrazolo[1,5-a]pyridin-4-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A59		3-(1'-((1H-indol-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

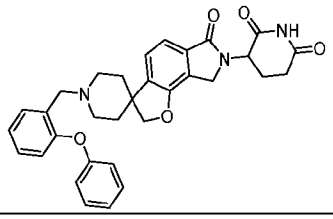
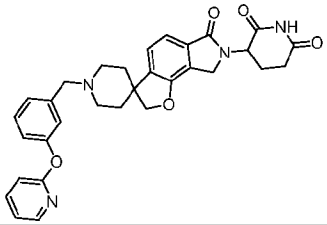
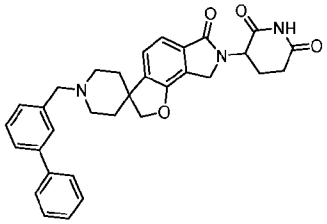
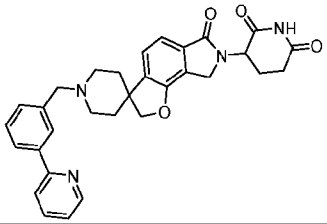
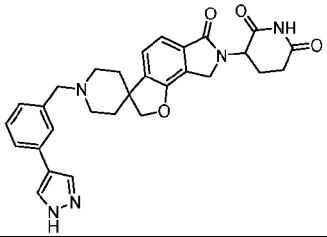
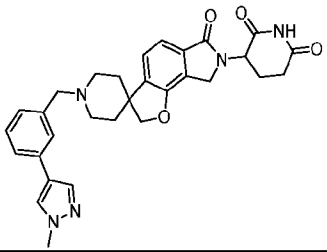
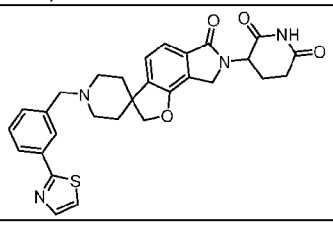
No.	Structure	Compound Name
A60		3-(1'-(benzo[d]isoxazol-5-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A62		3-(1'-(benzo[d]thiazol-6-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A64		3-(6-oxo-1'-(quinolin-7-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A65		3-(1'-(isoquinolin-6-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A66		3-(1'-((1H-pyrrolo[2,3-b]pyridin-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A67		3-(1'-((2-methyl-2H-indazol-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
A68		3-(1'-((2-methyl-2H-indazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A69		3-(1'-((2-methyl-2H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

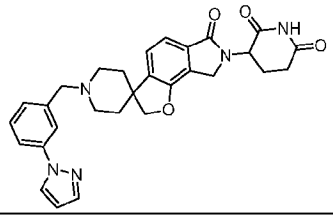
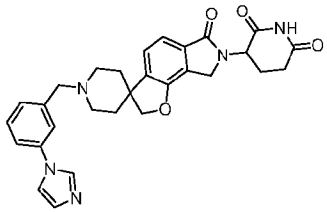
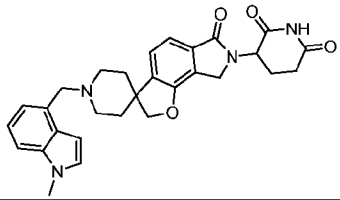
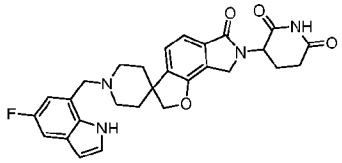
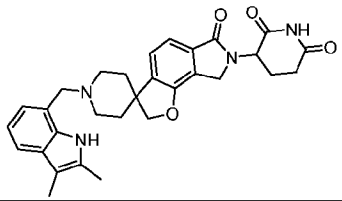
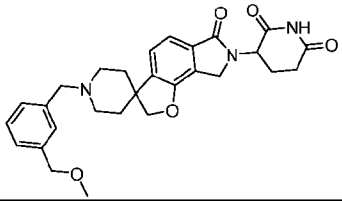
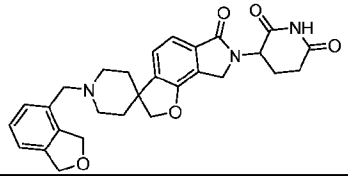
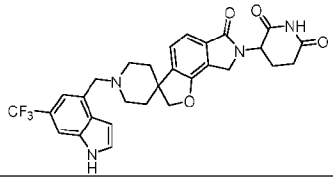
No.	Structure	Compound Name
A70		3-(1'-((1H-benzo[d]imidazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A71		3-(1'-((1H-benzo[d]imidazol-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A72		3-(1'-((1-methyl-1H-benzo[d]imidazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A73		3-(1'-((1H-pyrrolo[2,3-b]pyridin-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
A74		3-(1'-((1-methyl-1H-indol-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A75		3-(1'-((2-methyl-2H-indazol-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A76		3-(6-oxo-1'-(pyrazolo[1,5-a]pyridin-7-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A77		3-(1'-(imidazo[1,2-a]pyridin-8-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

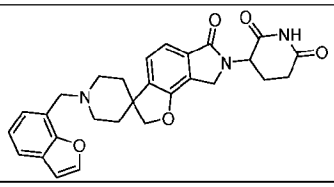
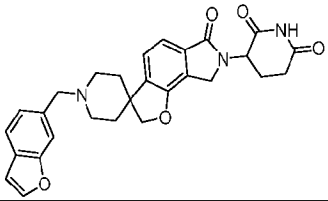
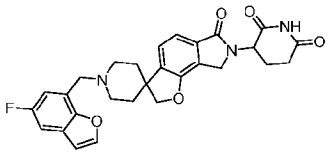
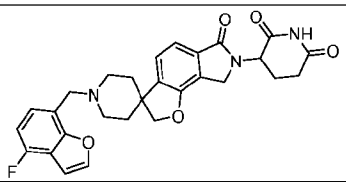
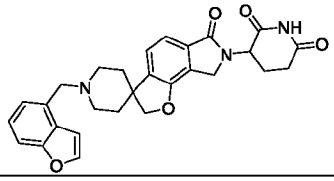
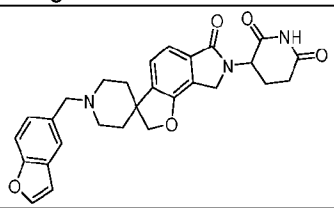
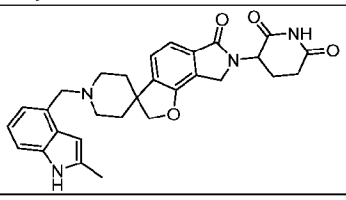
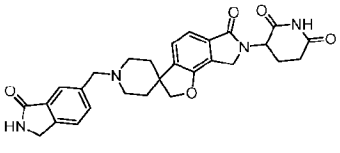
No.	Structure	Compound Name
A78		3-(1'-(imidazo[1,2-a]pyridin-7-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A79		3-(1'-(imidazo[1,2-a]pyridin-6-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A80		3-(6-oxo-1'-(pyrazolo[1,5-a]pyridin-5-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A81		3-(6-oxo-1'-((2-phenylthiazol-5-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A82		3-(6-oxo-1'-((2-phenylthiazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A83		3-(6-oxo-1'-((2-phenyloxazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A84		3-(6-oxo-1'-((2-phenyl-1H-imidazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A85		3-(6-oxo-1'-((4-phenylthiazol-2-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

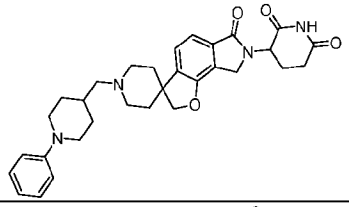
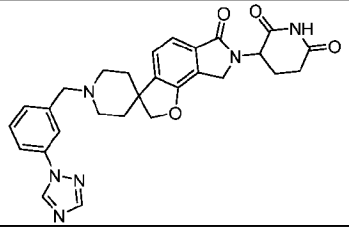
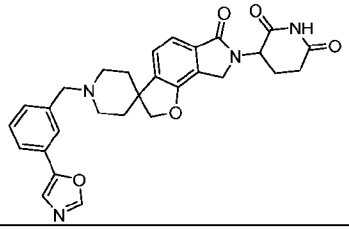
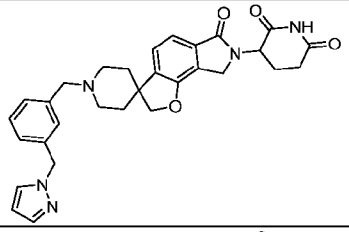
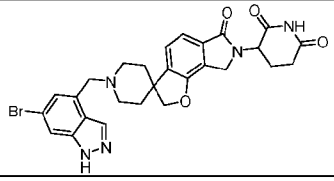
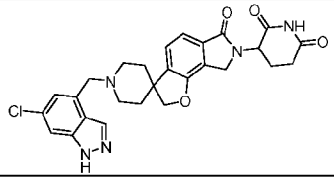
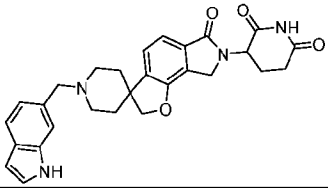
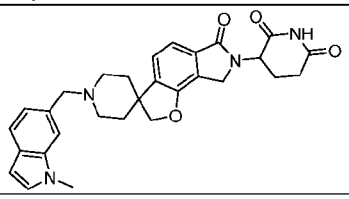
No.	Structure	Compound Name
A86		3-(6-oxo-1'-(3-phenoxybenzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A87		3-(1'-((1H-indol-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A88		3-(1'-(3-(tert-butyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A89		3-(6-oxo-1'-((4-phenylcyclohexyl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A90		3-(1'-(3-(difluoromethoxy)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A91		3-(1'-(3-bromobenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A92		3-(1'-(3-ethoxybenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

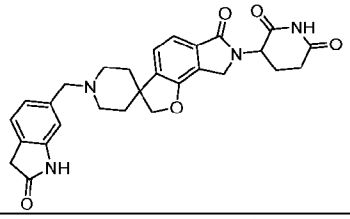
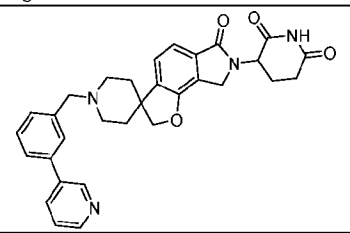
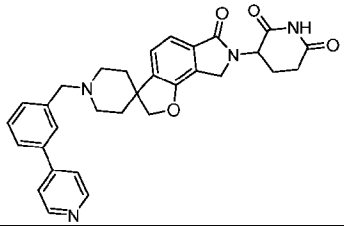
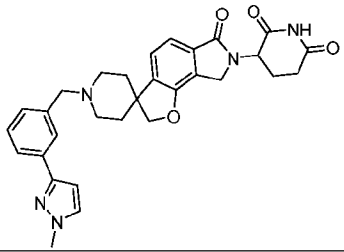
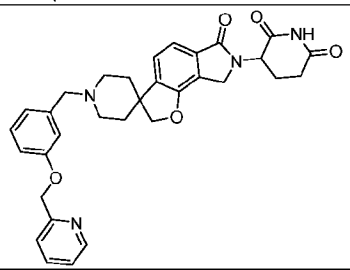
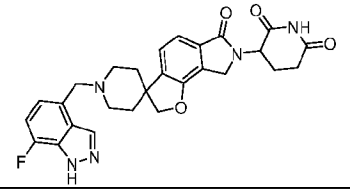
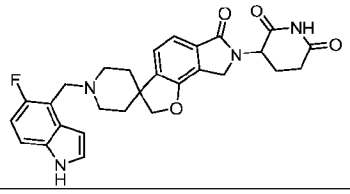
No.	Structure	Compound Name
A93		3-(1'-(3-(fluoromethyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A94		3-(1'-(3-(difluoromethyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A95		3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)-N-methylbenzamide
A96		3-(6-oxo-1'-(3-(pyrrolidin-1-yl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A97		3-(1'-(3-morpholinobenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A98		3-(1'-(3-(hydroxymethyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A99		3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)benzoic acid

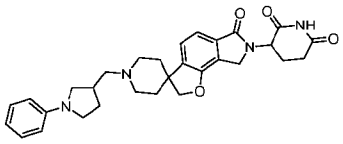
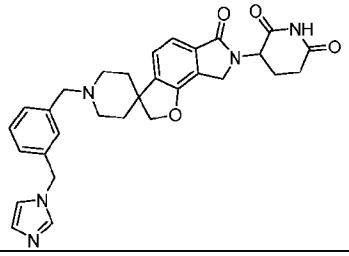
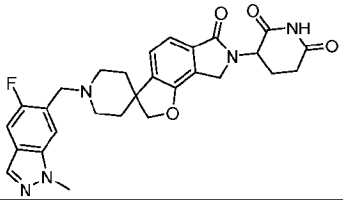
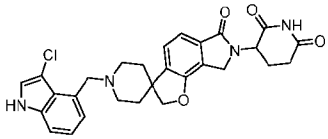
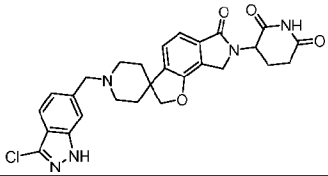
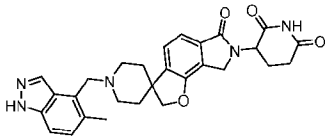
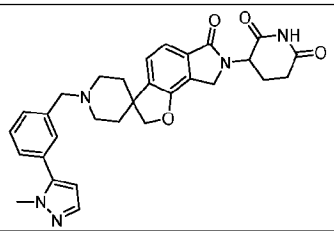
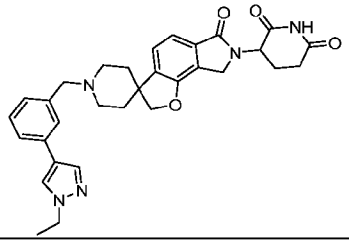
No.	Structure	Compound Name
A100		3-(6-oxo-1'-(2-phenoxybenzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A101		3-(6-oxo-1'-(3-(pyridin-2-yloxy)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A102		3-(1'-([1,1'-biphenyl]-3-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A103		3-(6-oxo-1'-(3-(pyridin-2-yl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A104		3-(1'-(3-(1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A105		3-(1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A106		3-(6-oxo-1'-(3-(thiazol-2-yl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

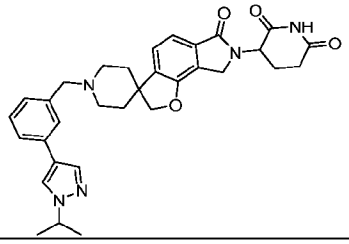
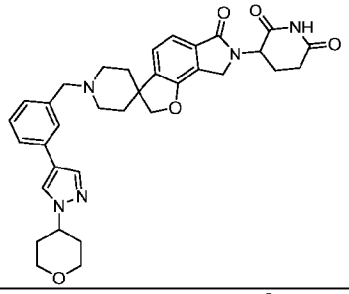
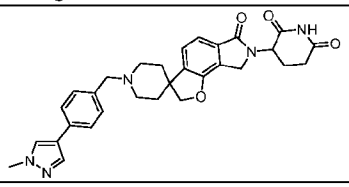
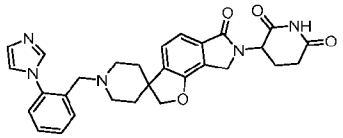
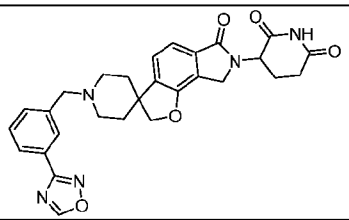
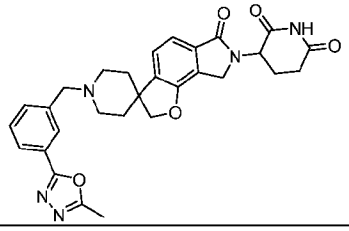
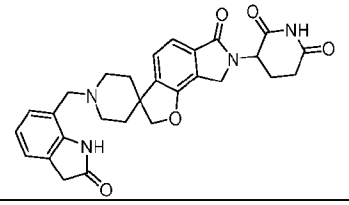
No.	Structure	Compound Name
A107		3-(1'-(3-(1H-pyrazol-1-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A108		3-(1'-(3-(1H-imidazol-1-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A109		3-(1'-((1-methyl-1H-indol-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
A110		3-(1'-((5-fluoro-1H-indol-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
A111		3-(1'-((2,3-dimethyl-1H-indol-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
A112		3-(1'-(3-(methoxymethyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A113		3-(1'-((1,3-dihydroisobenzofuran-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
A114		3-(6-oxo-1'-((6-(trifluoromethyl)-1H-indol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

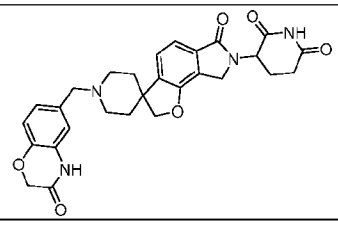
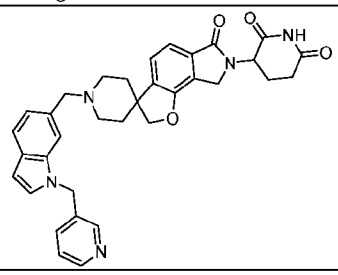
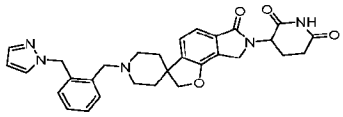
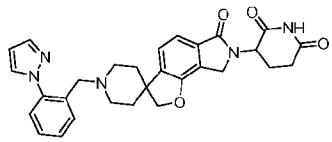
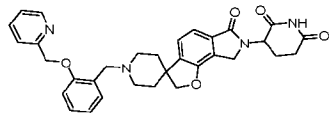
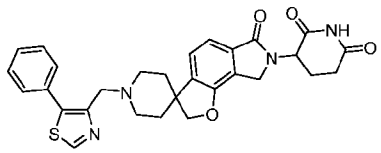
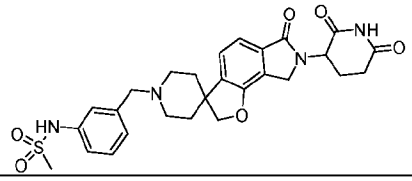
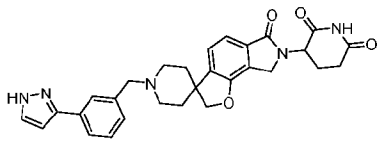
No.	Structure	Compound Name
A115		3-(1'-(benzofuran-7-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A116		3-(1'-(benzofuran-6-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A117		3-(1'-((5-fluorobenzofuran-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A118		3-(1'-((4-fluorobenzofuran-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
A119		3-(1'-(benzofuran-4-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A120		3-(1'-(benzofuran-5-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A121		3-(1'-((2-methyl-1H-indol-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
A122		3-(6-oxo-1'-((3-oxoisoindolin-5-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

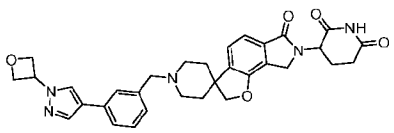
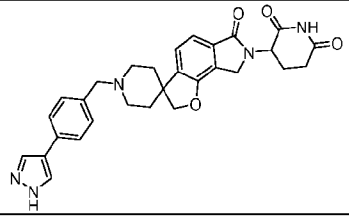
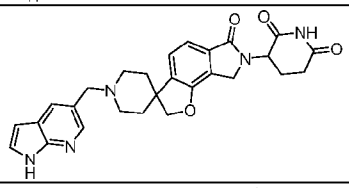
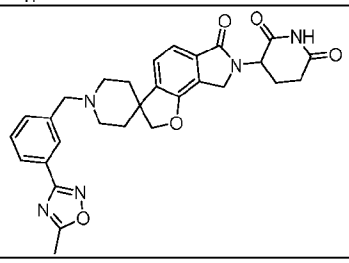
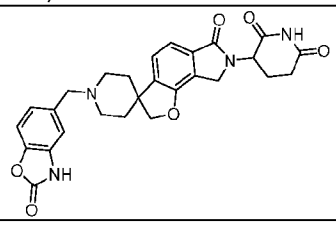
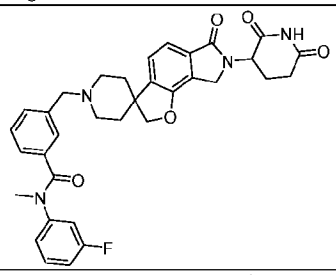
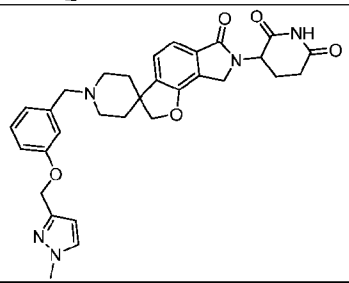
No.	Structure	Compound Name
A123		3-(6-oxo-1'-((1-phenylpiperidin-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A124		3-(1'-(3-(1H-1,2,4-triazol-1-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A125		3-(1'-(3-(oxazol-5-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A126		3-(1'-(3-((1H-pyrazol-1-yl)methyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A127		3-(1'-((6-bromo-1H-indazol-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
A128		3-(1'-((6-chloro-1H-indazol-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
A129		3-(1'-((1H-indol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A130		3-(1'-((1-methyl-1H-indol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

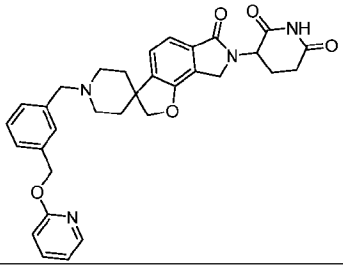
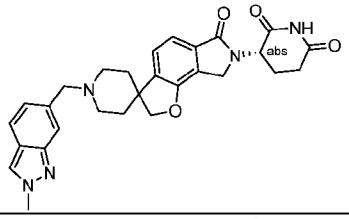
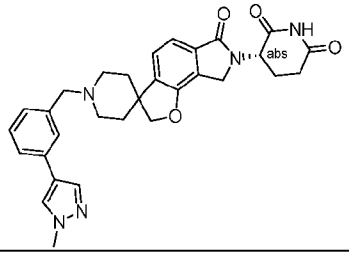
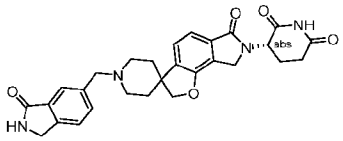
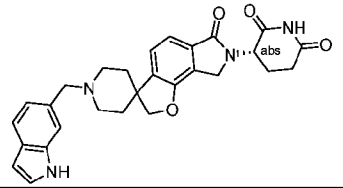
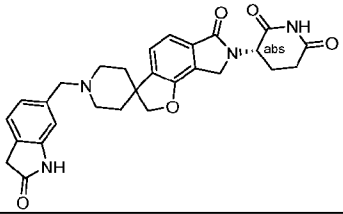
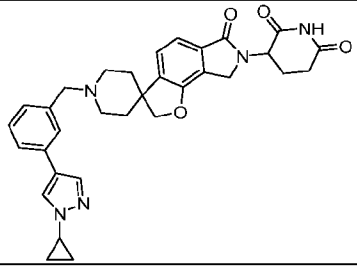
No.	Structure	Compound Name
A131		3-(6-oxo-1'-((2-oxoindolin-6-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A132		3-(6-oxo-1'-(3-(pyridin-3-yl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A133		3-(6-oxo-1'-(3-(pyridin-4-yl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A134		3-(1'-(3-(1-methyl-1H-pyrazol-3-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A135		3-(6-oxo-1'-(3-(pyridin-2-ylmethoxy)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A136		3-(1'-((7-fluoro-1H-indazol-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
A137		3-(1'-((5-fluoro-1H-indol-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

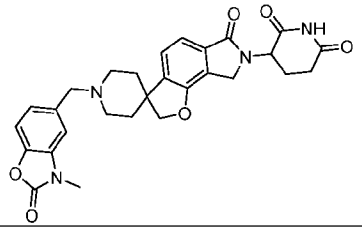
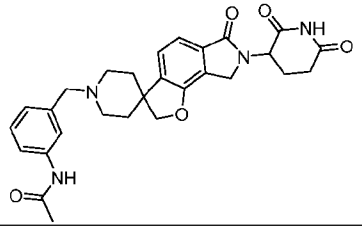
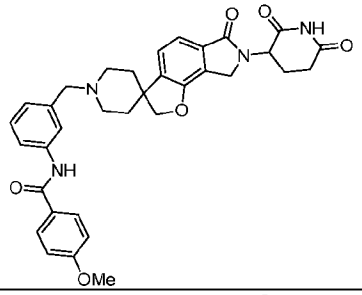
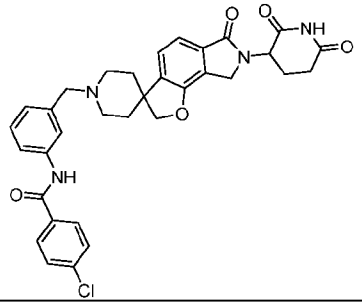
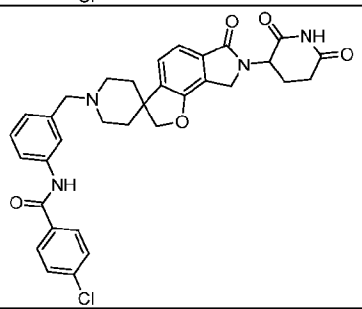
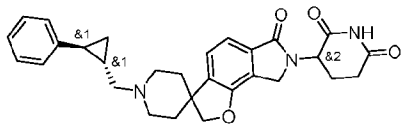
No.	Structure	Compound Name
A138		3-(6-oxo-1'-((1-phenylpyrrolidin-3-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A139		3-(1'-(3-((1H-imidazol-1-yl)methyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A140		3-(1'-((5-fluoro-1-methyl-1H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A141		3-(1'-((3-chloro-1H-indol-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
A142		3-(1'-((3-chloro-1H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A143		3-(1'-((5-methyl-1H-indazol-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
A144		3-(1'-(3-(1-methyl-1H-pyrazol-5-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A145		3-(1'-(3-(1-ethyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

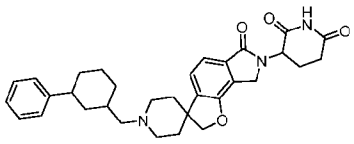
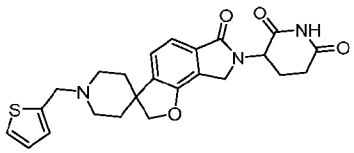
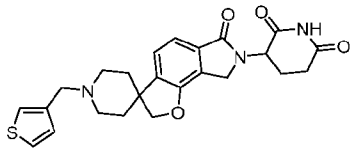
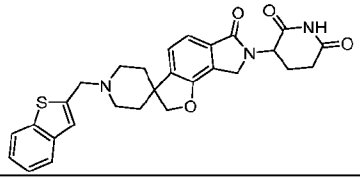
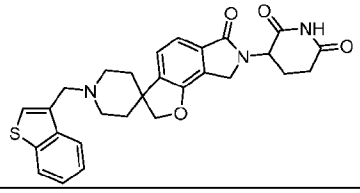
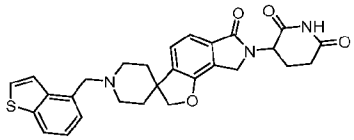
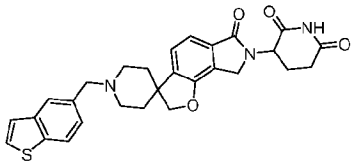
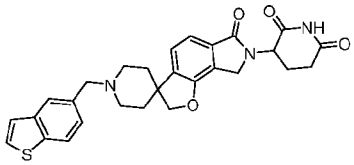
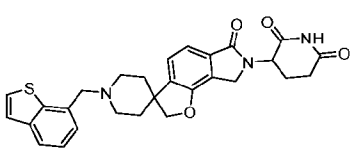
No.	Structure	Compound Name
A146		3-(1'-(3-(1-isopropyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A147		3-(6-oxo-1'-(3-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A148		3-(1'-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A149		3-(1'-(2-(1H-imidazol-1-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A150		3-(1'-(3-(1,2,4-oxadiazol-3-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A151		3-(1'-(3-(5-methyl-1,3,4-oxadiazol-2-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A152		3-(6-oxo-1'-((2-oxoindolin-7-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

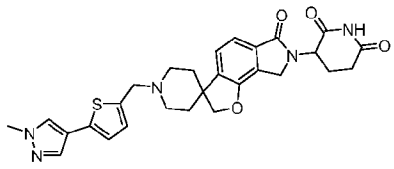
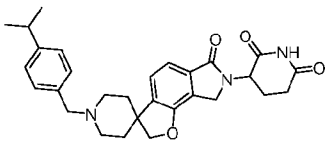
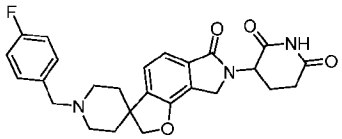
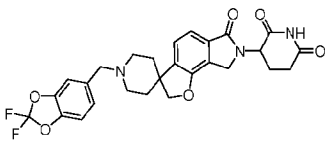
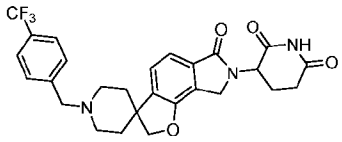
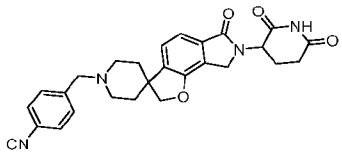
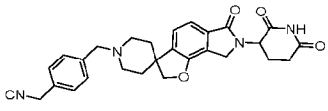
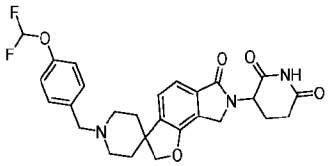
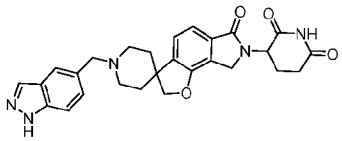
No.	Structure	Compound Name
A153		3-(6-oxo-1'-((3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A154		3-(6-oxo-1'-((1-(pyridin-3-ylmethyl)-1H-indol-6-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A155		3-(1'-(2-((1H-pyrazol-1-yl)methyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A156		3-(1'-(2-(1H-pyrazol-1-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A157		3-(6-oxo-1'-(2-(pyridin-2-ylmethoxy)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A158		3-(6-oxo-1'-((5-phenylthiazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A159		N-(3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)phenyl)methanesulfonamide
A160		3-(1'-(3-(1H-pyrazol-3-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

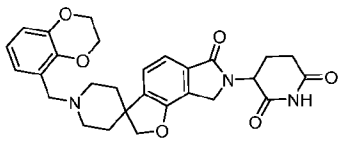
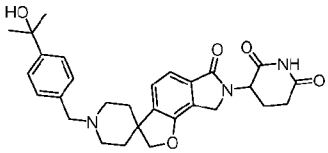
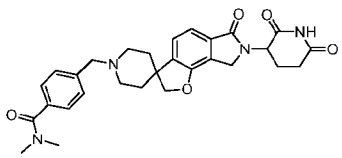
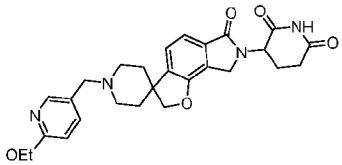
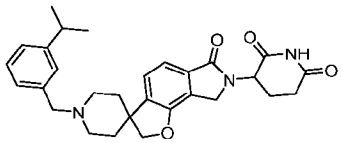
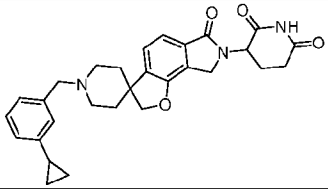
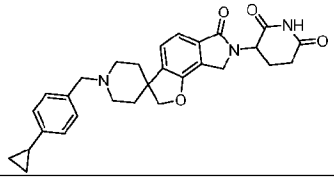
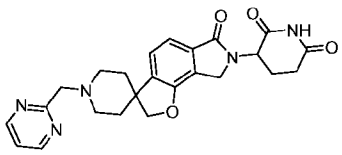
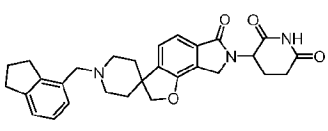
No.	Structure	Compound Name
A161		3-(1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A162		3-(1'-(4-(1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A163		3-(1'-((1H-pyrrolo[2,3-b]pyridin-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A164		3-(1'-(3-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A165		3-(6-oxo-1'-((2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A166		3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)-N-(3-fluorophenyl)-N-methylbenzamide
A167		3-(1'-(3-((1-methyl-1H-pyrazol-3-yl)methoxy)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

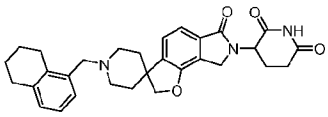
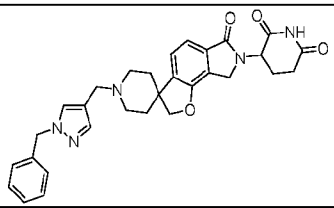
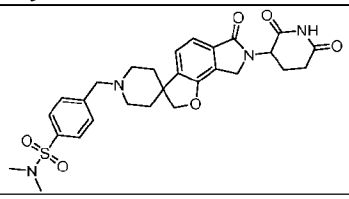
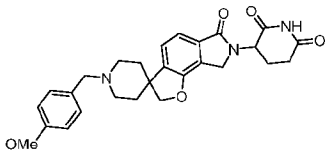
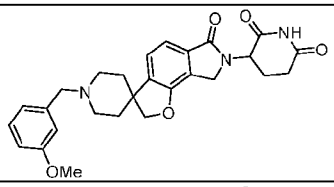
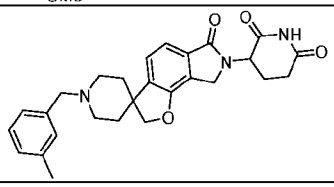
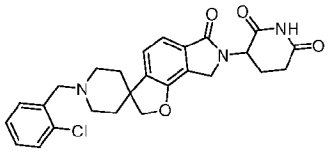
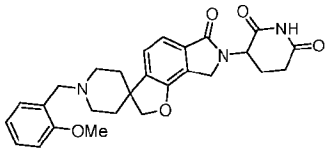
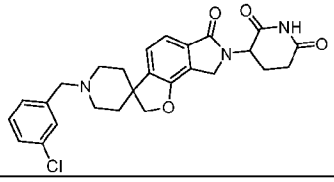
No.	Structure	Compound Name
A168		3-(6-oxo-1'-(3-((pyridin-2-yloxy)methyl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A169		(S)-3-(1'-((2-methyl-2H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A170		(S)-3-(1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A171		(S)-3-(6-oxo-1'-((3-oxoisoindolin-5-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A172		(S)-3-(1'-((1H-indol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A173		(S)-3-(6-oxo-1'-((2-oxoindolin-6-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A174		3-(1'-(3-(1-cyclopropyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

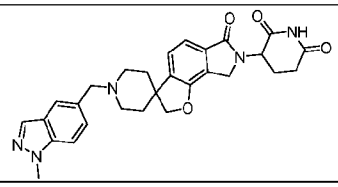
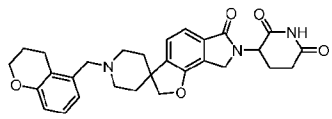
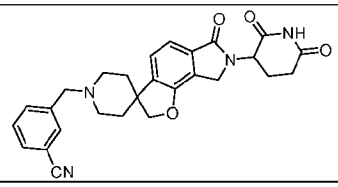
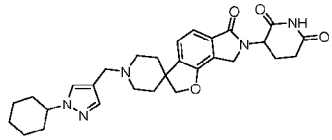
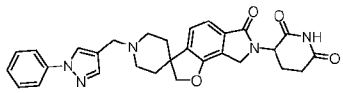
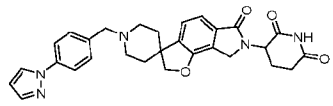
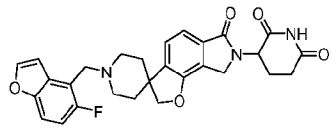
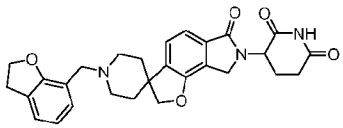
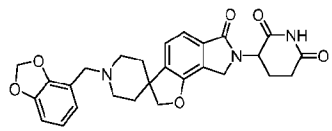
No.	Structure	Compound Name
A175		3-(1'-((3-methyl-2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A176		N-(3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)phenyl)acetamide
A177		N-(3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)phenyl)-4-methoxybenzamide
A178		4-chloro-N-(3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)phenyl)benzamide
A179		N-(3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)phenyl)-4-methylbenzamide
A180		3-(6-oxo-1'-((trans-2-phenylcyclopropyl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

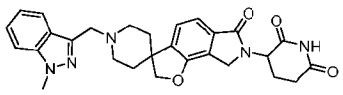
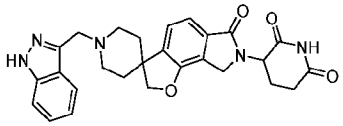
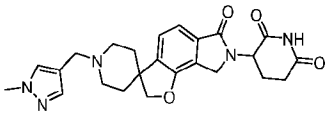
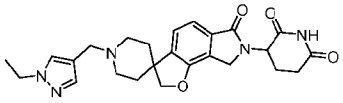
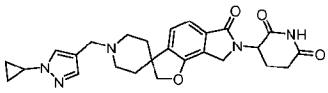
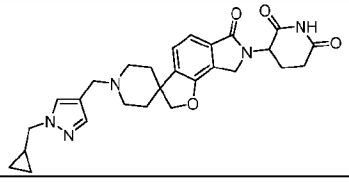
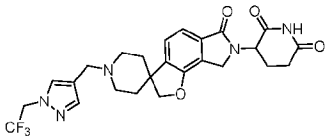
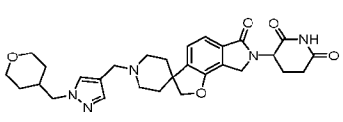
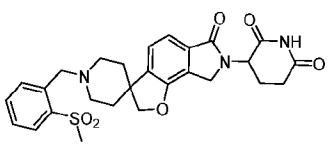
No.	Structure	Compound Name
A181		3-(6-oxo-1'-((3-phenylcyclohexyl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A182		3-(6-oxo-1'-(thiophen-2-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A183		3-(6-oxo-1'-(thiophen-3-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A184		3-(1'-(benzo[b]thiophen-2-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A185		3-(1'-(benzo[b]thiophen-3-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A186		3-(1'-(benzo[b]thiophen-4-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A187		3-(1'-(benzo[b]thiophen-5-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A188		3-(1'-(benzo[b]thiophen-6-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A189		3-(1'-(benzo[b]thiophen-7-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

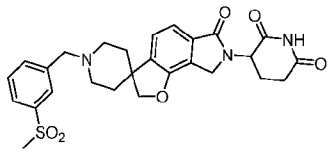
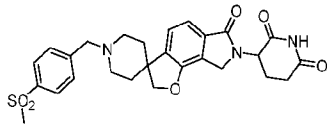
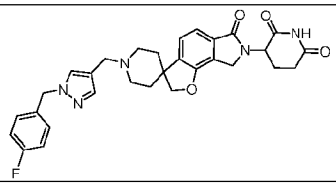
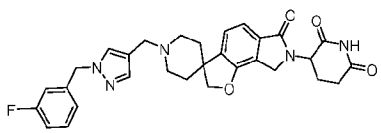
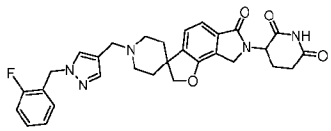
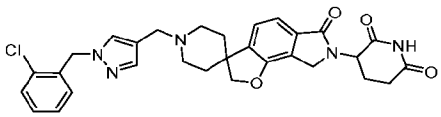
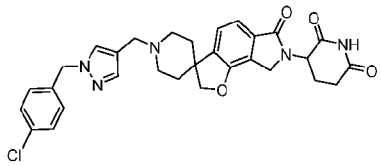
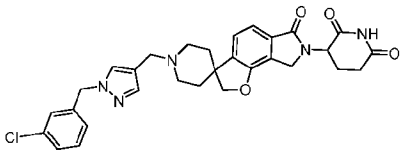
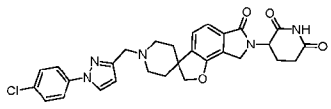
No.	Structure	Compound Name
A190		3-(1'-((5-(1-methyl-1H-pyrazol-4-yl)thiophen-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A191		3-(1'-(4-isopropylbenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A192		3-(1'-(4-fluorobenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A193		3-(1'-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A194		3-(6-oxo-1'-(4-(trifluoromethyl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A195		4-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)benzonitrile
A196		2-(4-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)phenyl)acetonitrile
A197		3-(1'-(4-(difluoromethoxy)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A198		3-(1'-((1H-indazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

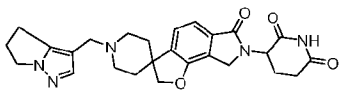
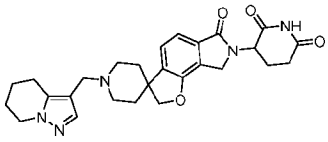
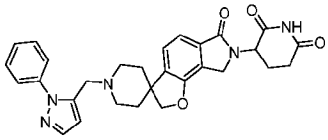
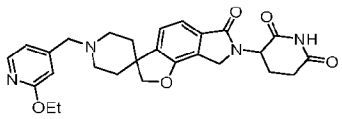
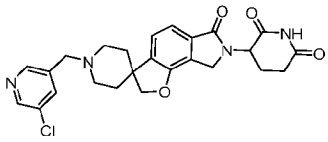
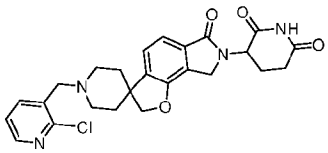
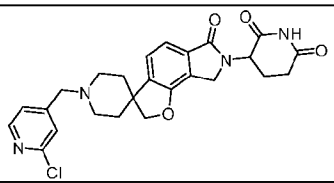
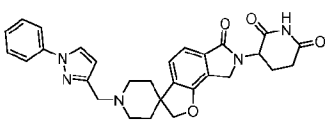
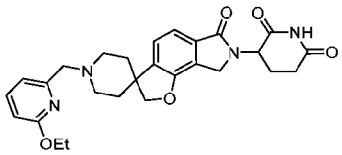
No.	Structure	Compound Name
A199		3-(1'-((2,3-dihydrobenzo[b][1,4]dioxin-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A200		3-(1'-(4-(2-hydroxypropan-2-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A201		4-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)-N,N-dimethylbenzamide
A202		3-(1'-((6-ethoxypyridin-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A203		3-(1'-(3-isopropylbenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A204		3-(1'-(3-cyclopropylbenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A205		3-(1'-(4-cyclopropylbenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A206		3-(6-oxo-1'-(pyrimidin-2-ylmethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A207		3-(1'-((2,3-dihydro-1H-inden-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

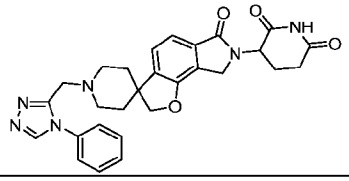
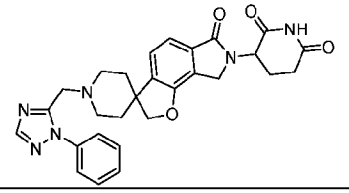
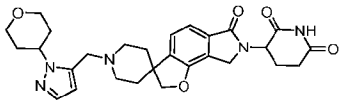
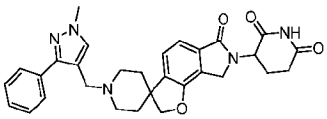
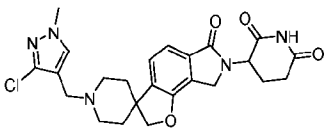
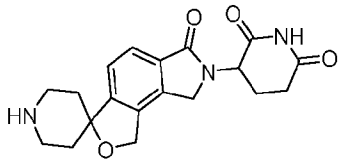
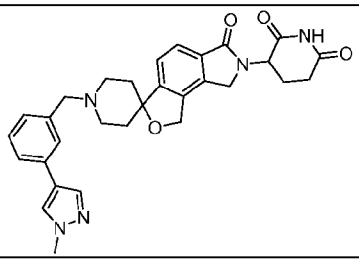
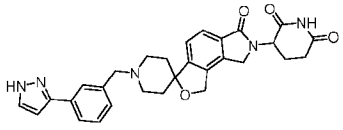
No.	Structure	Compound Name
A208		3-(6-oxo-1'-((5,6,7,8-tetrahydronaphthalen-1-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A209		3-(1'-((1-benzyl-1H-pyrazol-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A210		4-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)-N,N-dimethylbenzenesulfonamide
A211		3-(1'-(4-methoxybenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A212		3-(1'-(3-methoxybenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A213		3-(1'-(3-methylbenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A214		3-(1'-(2-chlorobenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A215		3-(1'-(2-methoxybenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A216		3-(1'-(3-chlorobenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

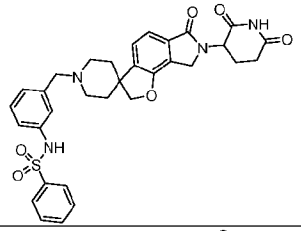
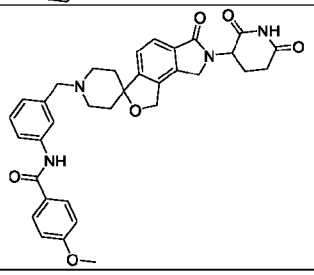
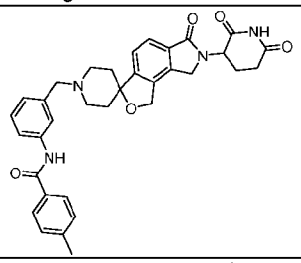
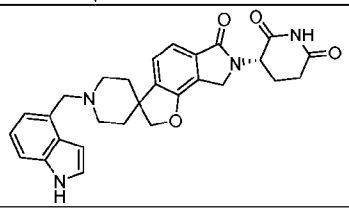
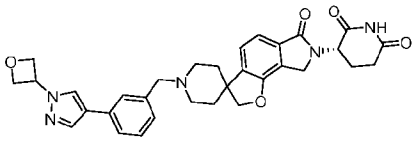
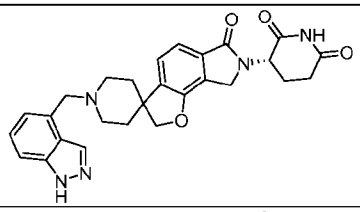
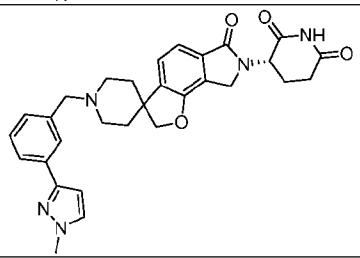
No.	Structure	Compound Name
A217		3-(1'-((1-methyl-1H-indazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A218		3-(1'-(chroman-5-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A219		3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)benzonitrile
A220		3-(1'-((1-cyclohexyl-1H-pyrazol-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
A221		3-(6-oxo-1'-((1-phenyl-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A222		3-(1'-(4-(1H-pyrazol-1-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A223		3-(1'-((5-fluorobenzofuran-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
A224		3-(1'-((2,3-dihydrobenzofuran-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
A225		3-(1'-(benzo[d][1,3]dioxol-4-ylmethyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

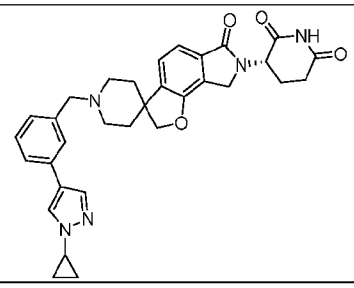
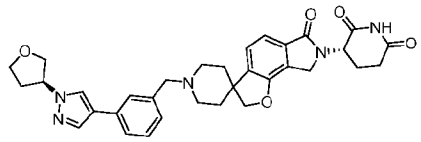
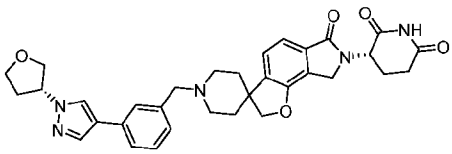
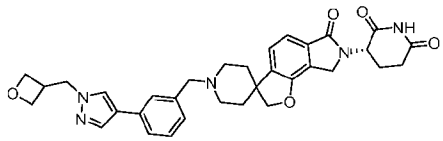
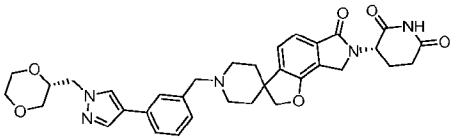
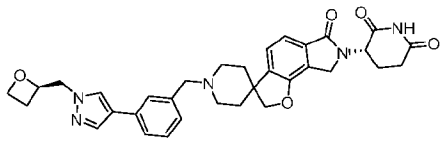
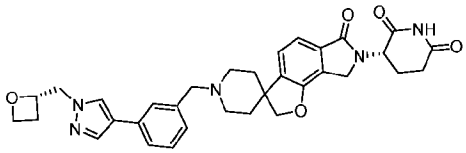
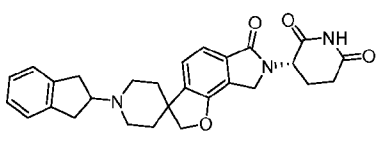
No.	Structure	Compound Name
A226		3-(1'-((1-methyl-1H-indazol-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A227		3-(1'-((1H-indazol-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A228		3-(1'-((1-methyl-1H-pyrazol-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
A229		3-(1'-((1-ethyl-1H-pyrazol-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
A230		3-(1'-((1-cyclopropyl-1H-pyrazol-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
A231		3-(1'-((1-(cyclopropylmethyl)-1H-pyrazol-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
A232		3-(6-oxo-1'-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A233		3-(6-oxo-1'-((1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A234		3-(1'-(2-(methylsulfonyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

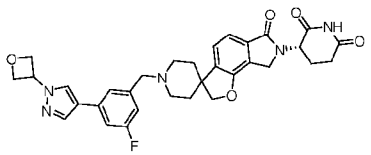
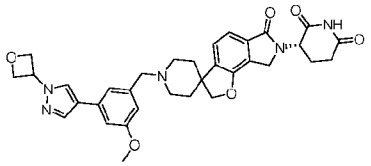
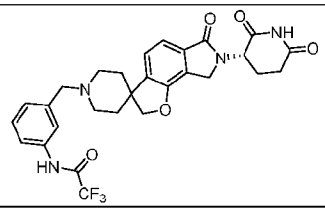
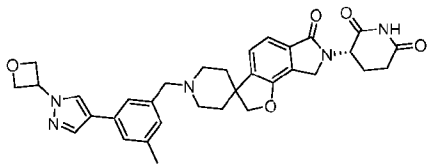
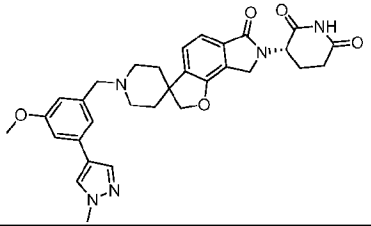
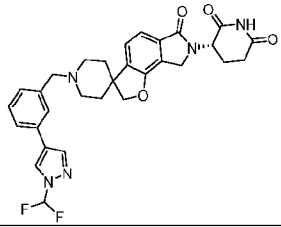
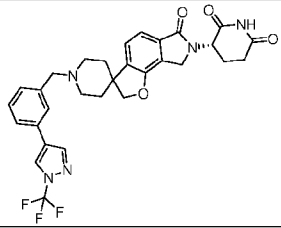
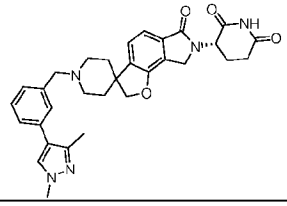
No.	Structure	Compound Name
A235		3-(1'-(3-(methylsulfonyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A236		3-(1'-(4-(methylsulfonyl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A237		3-(1'-((1-(4-fluorobenzyl)-1H-pyrazol-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A238		3-(1'-((1-(3-fluorobenzyl)-1H-pyrazol-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
A239		3-(1'-((1-(2-fluorobenzyl)-1H-pyrazol-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
A240		3-(1'-((1-(2-chlorobenzyl)-1H-pyrazol-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
A241		3-(1'-((1-(4-chlorobenzyl)-1H-pyrazol-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
A242		3-(1'-((1-(3-chlorobenzyl)-1H-pyrazol-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
A243		3-(1'-((1-(4-chlorophenyl)-1H-pyrazol-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

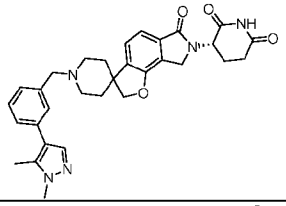
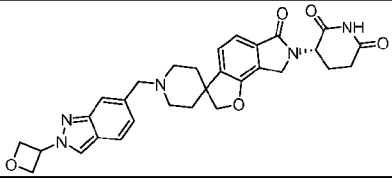
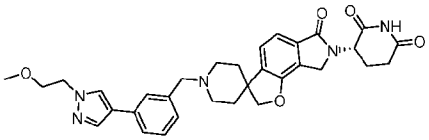
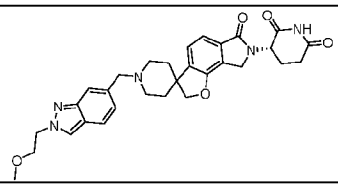
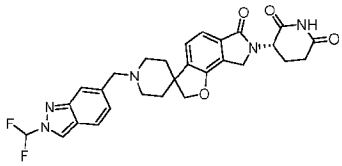
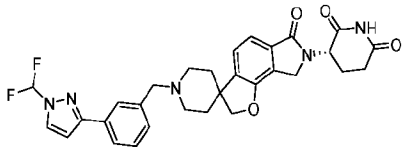
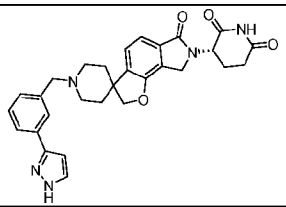
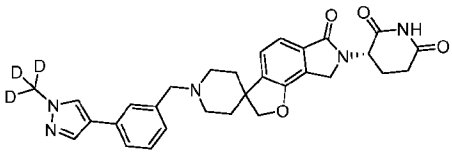
No.	Structure	Compound Name
A244		3-(1'-((5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A245		3-(6-oxo-1'-((4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A246		3-(6-oxo-1'-((1-phenyl-1H-pyrazol-5-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A247		3-(1'-((2-ethoxypyridin-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
A248		3-(1'-((5-chloropyridin-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
A249		3-(1'-((2-chloropyridin-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
A250		3-(1'-((2-chloropyridin-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
A251		3-(6-oxo-1'-((1-phenyl-1H-pyrazol-3-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A252		3-(1'-((6-ethoxypyridin-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

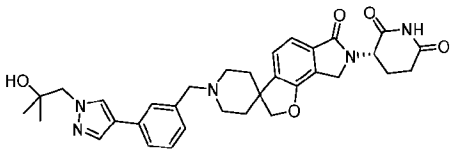
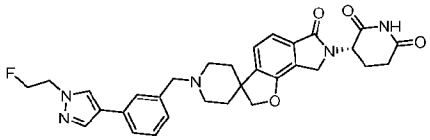
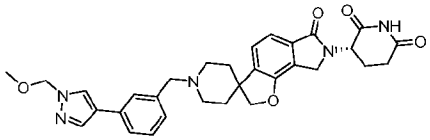
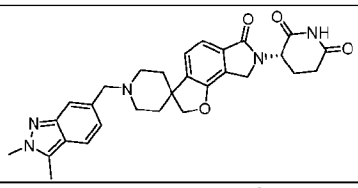
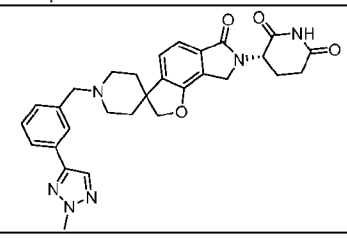
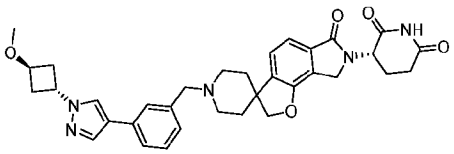
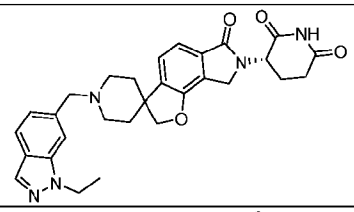
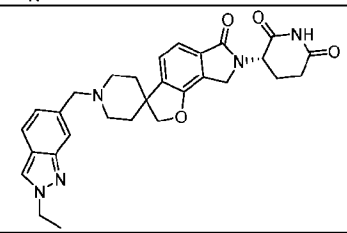
No.	Structure	Compound Name
A253		3-(6-oxo-1'-((4-phenyl-4H-1,2,4-triazol-3-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A254		3-(6-oxo-1'-((1-phenyl-1H-1,2,4-triazol-5-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A255		3-(6-oxo-1'-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-5-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A256		3-(1'-((1-methyl-3-phenyl-1H-pyrazol-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
A257		3-(1'-((3-chloro-1-methyl-1H-pyrazol-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
A258		3-(6-oxo-6,8-dihydrospiro[furo[3,4-e]isoindole-3,4'-piperidin]-7(1H)-yl)piperidine-2,6-dione
A259		3-(1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydrospiro[furo[3,4-e]isoindole-3,4'-piperidin]-7(1H)-yl)piperidine-2,6-dione
A260		3-(1'-(3-(1H-pyrazol-3-yl)benzyl)-6-oxo-6,8-dihydrospiro[furo[3,4-e]isoindole-3,4'-piperidin]-7(1H)-yl)piperidine-2,6-dione

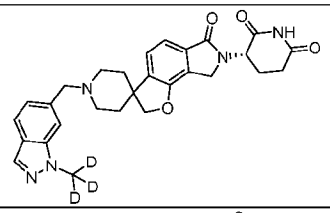
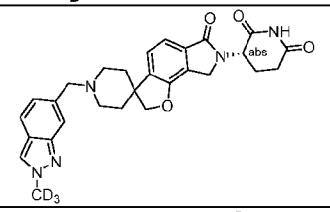
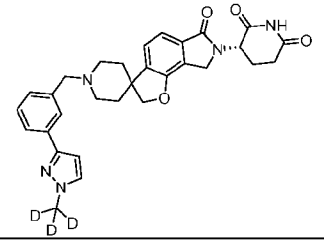
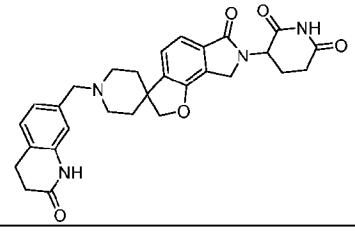
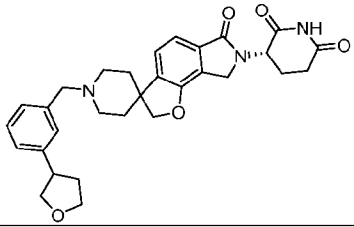
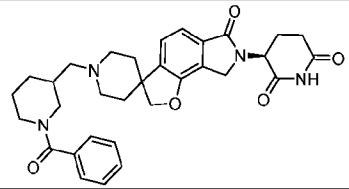
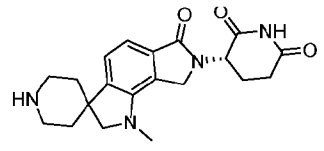
No.	Structure	Compound Name
A261		N-(3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)phenyl)benzenesulfonamide
A262		N-(3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-1,6,7,8-tetrahydrospiro[furo[3,4-e]isoindole-3,4'-piperidin]-1'-yl)methyl)phenyl)-4-methoxybenzamide
A263		N-(3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-1,6,7,8-tetrahydrospiro[furo[3,4-e]isoindole-3,4'-piperidin]-1'-yl)methyl)phenyl)-4-methylbenzamide
A264		(S)-3-(1'-((1H-indol-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
A265		(S)-3-(1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A266		(S)-3-(1'-((1H-indazol-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
A267		(S)-3-(1'-(3-(1-methyl-1H-pyrazol-3-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

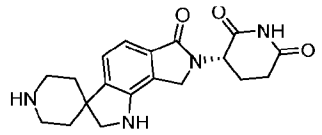
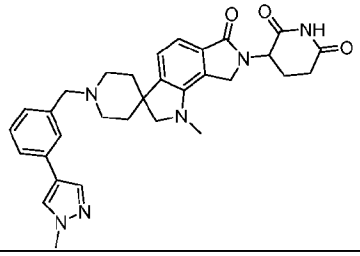
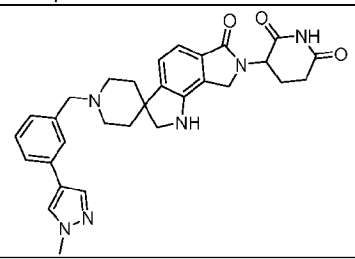
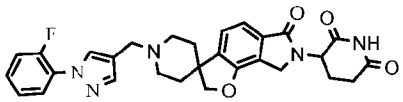
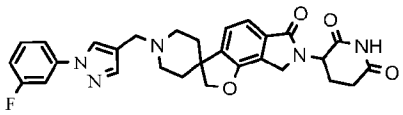
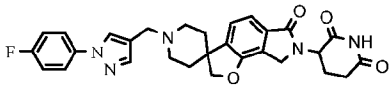
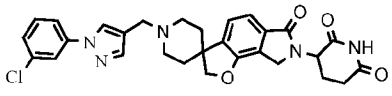
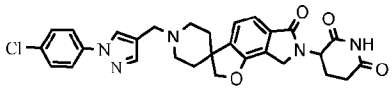
No.	Structure	Compound Name
A268		(S)-3-(1'-(3-(1-cyclopropyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A269		(S)-3-(6-oxo-1'-(3-(1-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A270		(S)-3-(6-oxo-1'-(3-(1-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-4-yl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A271		(S)-3-(1'-(3-(1-(oxetan-3-ylmethyl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A272		(S)-3-(1'-(3-(1-(((R)-1,4-dioxan-2-yl)methyl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A273		(S)-3-(1'-(3-(1-(((R)-oxetan-2-yl)methyl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A274		(S)-3-(1'-(3-(1-(((S)-oxetan-2-yl)methyl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A275		(S)-3-(1'-(2,3-dihydro-1H-inden-2-yl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

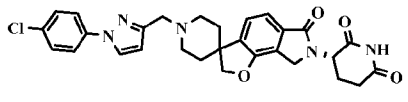
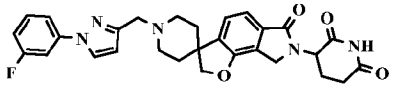
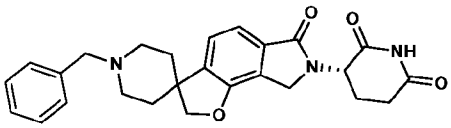
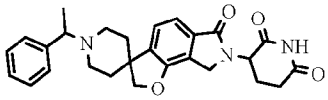
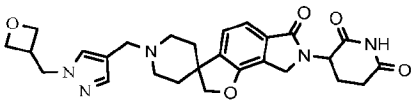
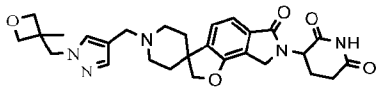
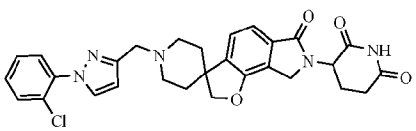
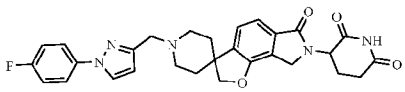
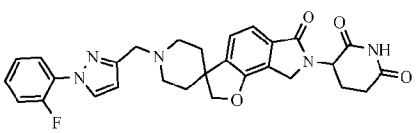
No.	Structure	Compound Name
A276		(S)-3-(1'-(3-fluoro-5-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A277		(S)-3-(1'-(3-methoxy-5-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A278		(S)-N-(3-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)phenyl)-2,2,2-trifluoroacetamide
A279		(S)-3-(1'-(3-methyl-5-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A280		(S)-3-(1'-(3-methoxy-5-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A281		(S)-3-(1'-(3-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A282		(S)-3-(6-oxo-1'-(3-(1-(trifluoromethyl)-1H-pyrazol-4-yl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A283		(S)-3-(1'-(3-(1,3-dimethyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

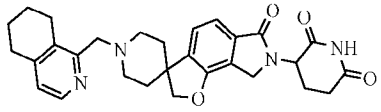
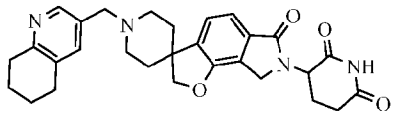
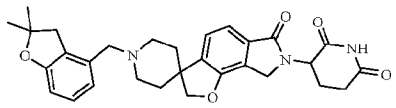
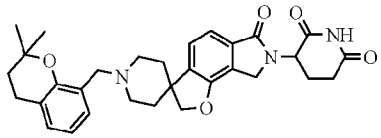
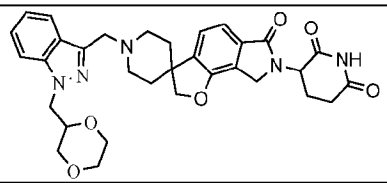
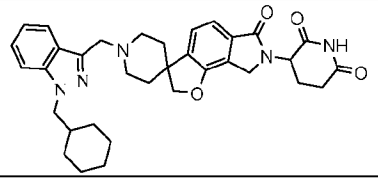
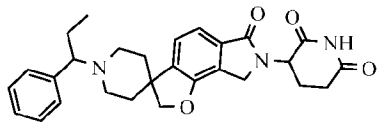
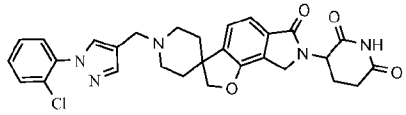
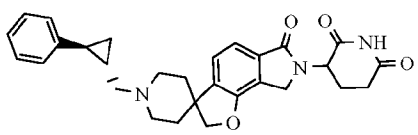
No.	Structure	Compound Name
A284		(S)-3-(1'-(3-(1,5-dimethyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A285		(S)-3-(1'-((2-(oxetan-3-yl)-2H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A286		(S)-3-(1'-(3-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A287		(S)-3-(1'-((2-(2-methoxyethyl)-2H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A288		(S)-3-(1'-((2-(difluoromethyl)-2H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A289		(S)-3-(1'-(3-(1-(difluoromethyl)-1H-pyrazol-3-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A290		(S)-3-(1'-(3-(1H-pyrazol-3-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A291		(S)-3-(1'-(3-(1-(methyl-d3)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

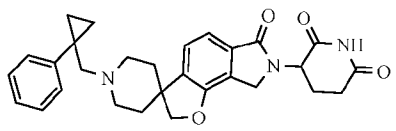
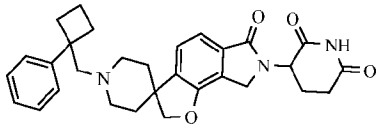
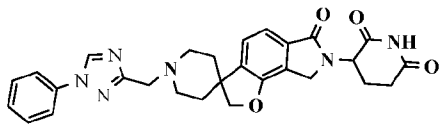
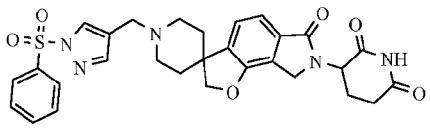
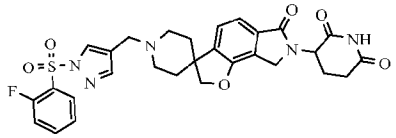
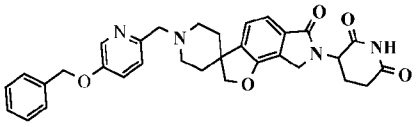
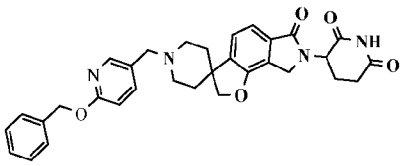
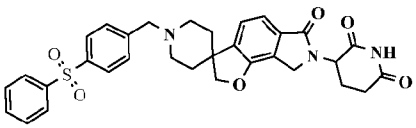
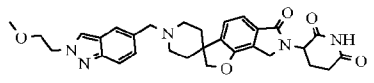
No.	Structure	Compound Name
A292		(S)-3-(1'-(3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A293		(S)-3-(1'-(3-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A294		(S)-3-(1'-(3-(1-(methoxymethyl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A295		(S)-3-(1'-((2,3-dimethyl-2H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A296		(S)-3-(1'-(3-(2-methyl-2H-1,2,3-triazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A297		(S)-3-(1'-(3-(1-((1r,3r)-3-methoxycyclobutyl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A298		(S)-3-(1'-((1-ethyl-1H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A299		(S)-3-(1'-((2-ethyl-2H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

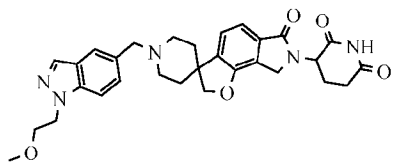
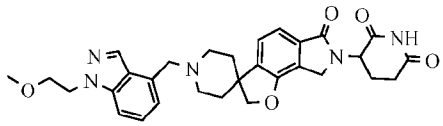
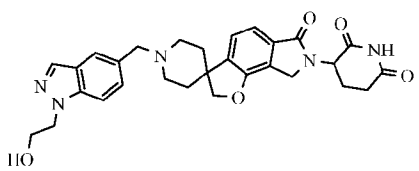
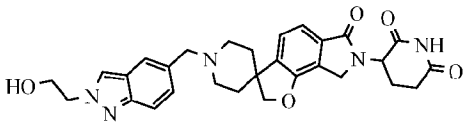
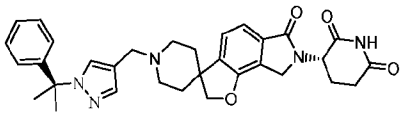
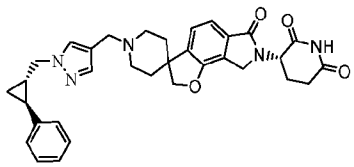
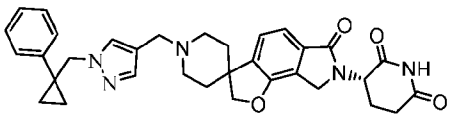
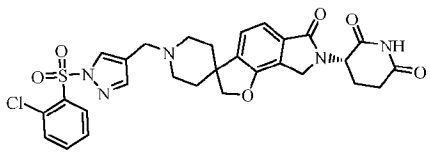
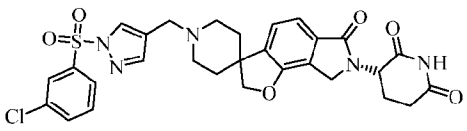
No.	Structure	Compound Name
A300		(S)-3-(1'-((1-(methyl-d3)-1H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A301		(S)-3-(1'-((2-(methyl-d3)-2H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A302		(S)-3-(1'-(3-(1-(methyl-d3)-1H-pyrazol-3-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A303		3-(6-oxo-1'-((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A304		(3S)-3-(6-oxo-1'-(3-(tetrahydrofuran-3-yl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A305		(3S)-3-(1'-((1-benzoylpiperidin-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
A306		(S)-3-(1'-methyl-6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)piperidine-2,6-dione

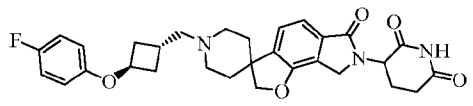
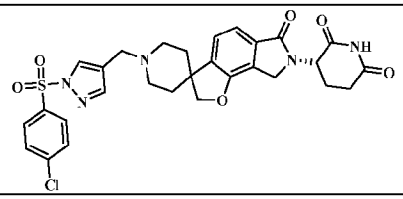
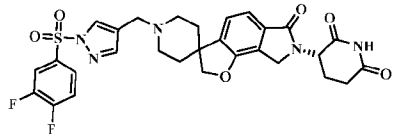
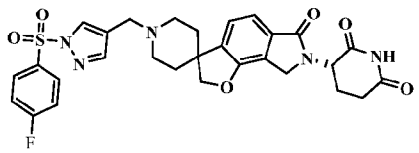
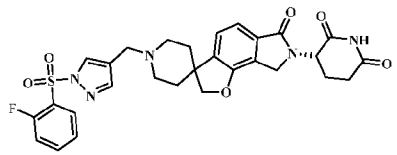
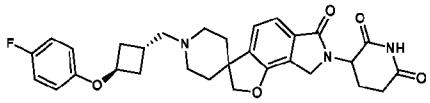
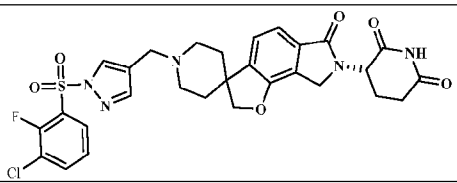
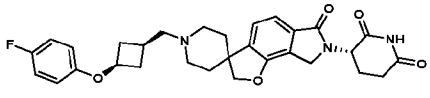
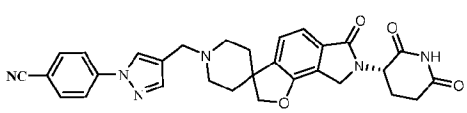
No.	Structure	Compound Name
A307		(S)-3-(6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)piperidine-2,6-dione
A308		3-(1'-methyl-1-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)piperidine-2,6-dione
A309		3-(1-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)piperidine-2,6-dione
A310		3-(1'-((1-(2-fluorophenyl)-1H-pyrazol-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
A311		3-(1'-((1-(3-fluorophenyl)-1H-pyrazol-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
A312		3-(1'-((1-(4-fluorophenyl)-1H-pyrazol-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
A313		3-(1'-((1-(3-chlorophenyl)-1H-pyrazol-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
A314		3-(1'-((1-(4-chlorophenyl)-1H-pyrazol-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

No.	Structure	Compound Name
A315		(S)-3-(1'-((1-(4-chlorophenyl)-1H-pyrazol-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
A316		3-(1'-((1-(3-fluorophenyl)-1H-pyrazol-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
A317		(S)-3-(1'-benzyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A318		3-(6-oxo-1'-(1-phenylethyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A319		3-(1'-((1-(oxetan-3-ylmethyl)-1H-pyrazol-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
A320		3-(1'-((1-((3-methyloxetan-3-yl)methyl)-1H-pyrazol-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
A321		3-(1'-((1-(2-chlorophenyl)-1H-pyrazol-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
A322		3-(1'-((1-(4-fluorophenyl)-1H-pyrazol-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
A323		3-(1'-((1-(2-fluorophenyl)-1H-pyrazol-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

No.	Structure	Compound Name
A324		3-(6-oxo-1'-((5,6,7,8-tetrahydroisoquinolin-1-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A325		3-(6-oxo-1'-((5,6,7,8-tetrahydroquinolin-3-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A326		3-(1'-((2,2-dimethyl-2,3-dihydrobenzofuran-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
A327		3-(1'-((2,2-dimethylchroman-8-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A328		3-(1'-((1-((1,4-dioxan-2-yl)methyl)-1H-indazol-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
A329		3-(1'-((1-(cyclohexylmethyl)-1H-indazol-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
A330		3-(6-oxo-1'-(1-phenylpropyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A331		3-(1'-((1-(2-chlorophenyl)-1H-pyrazol-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
A332		3-(6-oxo-1'-(((1S,2S)-2-phenylcyclopropyl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

No.	Structure	Compound Name
A333		3-(6-oxo-1'-((1-phenylcyclopropyl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A334		3-(6-oxo-1'-((1-phenylcyclobutyl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A335		3-(6-oxo-1'-((1-phenyl-1H-1,2,4-triazol-3-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A336		3-(6-oxo-1'-((1-(phenylsulfonyl)-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A337		3-(1'-((1-((2-fluorophenyl)sulfonyl)-1H-pyrazol-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
A338		3-(1'-((5-(benzyloxy)pyridin-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
A339		3-(1'-((6-(benzyloxy)pyridin-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
A340		3-(6-oxo-1'-(4-(phenylsulfonyl)benzyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A341		3-(1'-((2-(2-methoxyethyl)-2H-indazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

No.	Structure	Compound Name
A342		3-(1'-((1-(2-methoxyethyl)-1H-indazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A343		3-(1'-((1-(2-methoxyethyl)-1H-indazol-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
A344		3-(1'-((1-(2-hydroxyethyl)-1H-indazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A345		3-(1'-((2-(2-hydroxyethyl)-2H-indazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A346		(S)-3-(6-oxo-1'-((1-(2-phenylpropan-2-yl)-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A347		(S)-3-(6-oxo-1'-((1-(((1S,2S)-2-phenylcyclopropyl)methyl)-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A348		(S)-3-(6-oxo-1'-((1-((1-phenylcyclopropyl)methyl)-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A349		(S)-3-(1'-((1-((2-chlorophenyl)sulfonyl)-1H-pyrazol-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
A350		(S)-3-(1'-((1-((3-chlorophenyl)sulfonyl)-1H-pyrazol-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

No.	Structure	Compound Name
A351		3-(1'-(((1r,3r)-3-(4-fluorophenoxy)cyclobutyl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A352		(S)-3-(1'-((1-((4-chlorophenyl)sulfonyl)-1H-pyrazol-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
A353		(S)-3-(1'-((1-((3,4-difluorophenyl)sulfonyl)-1H-pyrazol-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
A354		(S)-3-(1'-((1-((4-fluorophenyl)sulfonyl)-1H-pyrazol-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
A355		(S)-3-(1'-((1-((2-fluorophenyl)sulfonyl)-1H-pyrazol-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
A356		3-(1'-(((1r,3r)-3-(4-fluorophenoxy)cyclobutyl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A357		(S)-3-(1'-((1-((3-chloro-2-fluorophenyl)sulfonyl)-1H-pyrazol-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
A358		(S)-3-(1'-(((1s,3R)-3-(4-fluorophenoxy)cyclobutyl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A359		(S)-4-(4-((7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)-1H-pyrazol-1-yl)benzonitrile

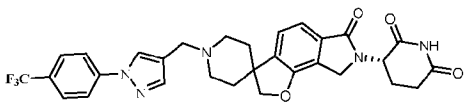
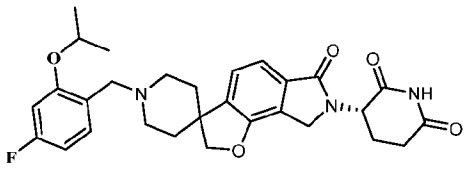
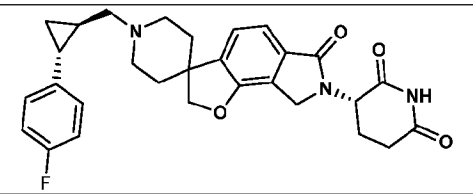
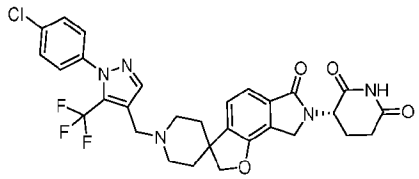
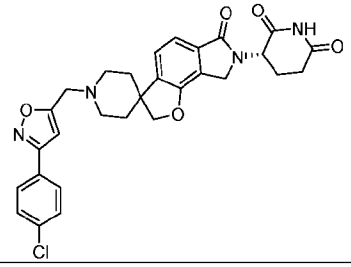
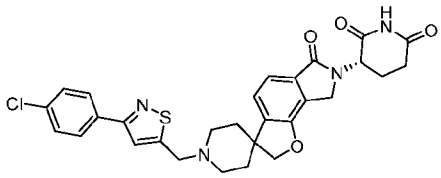
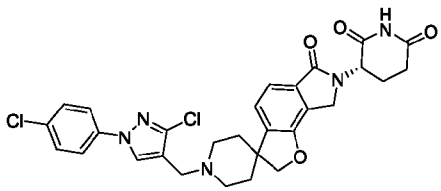
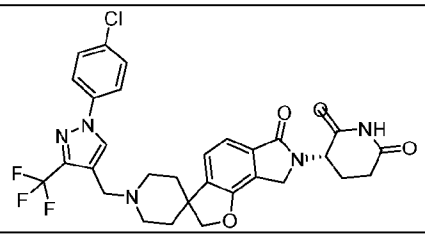
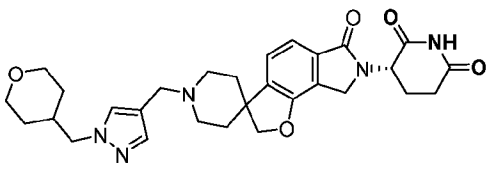
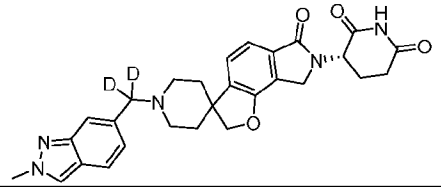
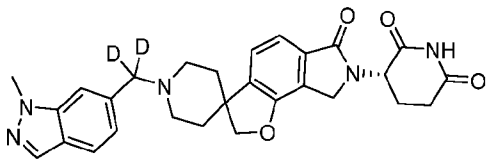
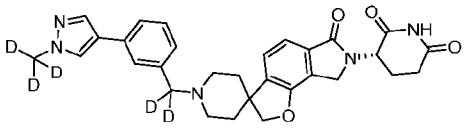
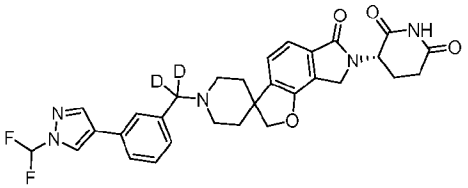
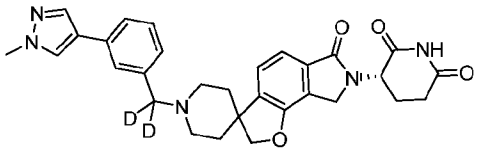
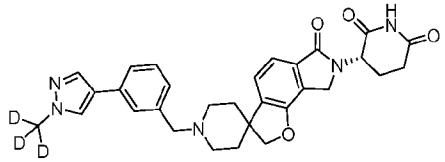
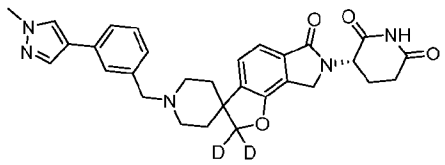
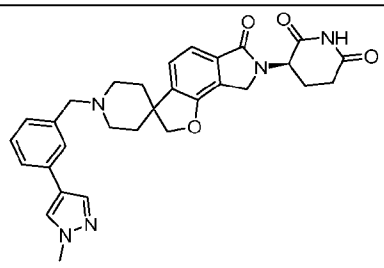
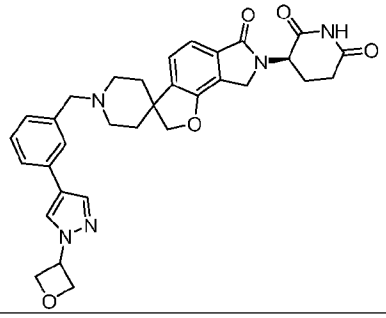
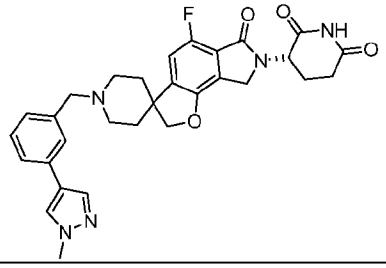
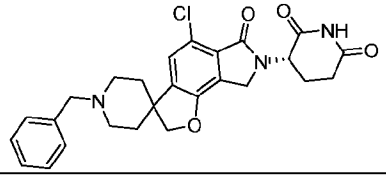
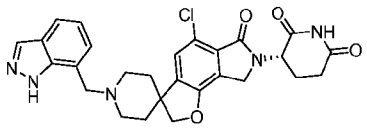
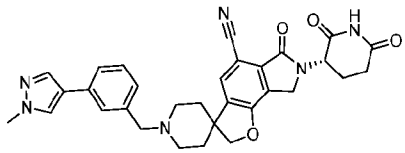
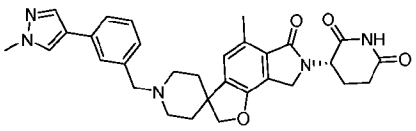
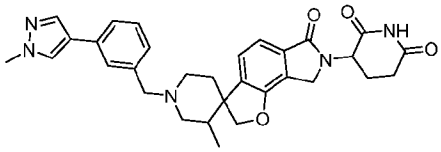
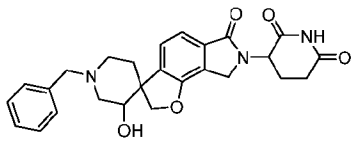
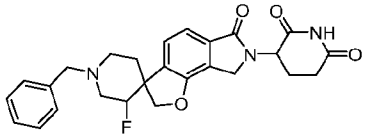
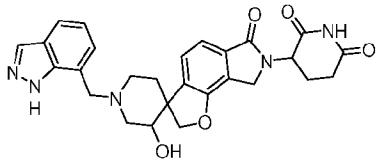
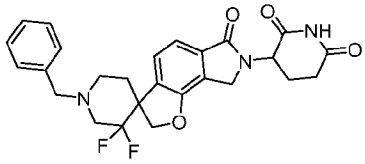
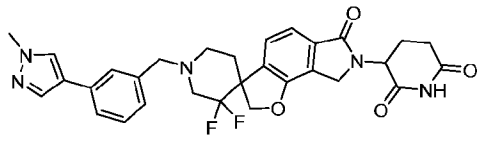
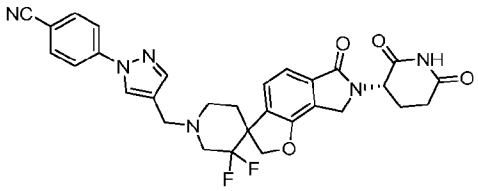
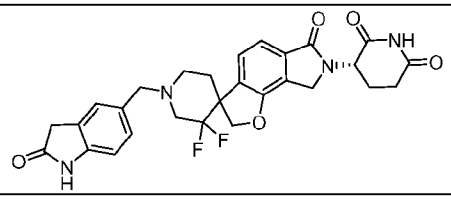
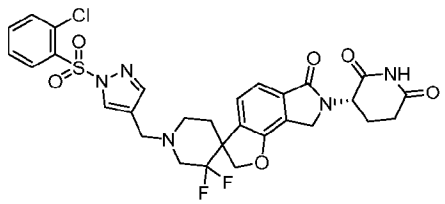
No.	Structure	Compound Name
A360		(S)-3-(6-oxo-1'-((1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A361		(S)-3-(1'-(4-fluoro-2-isopropoxybenzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A362		(S)-3-(1'-(((1R,2R)-2-(4-fluorophenyl)cyclopropyl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

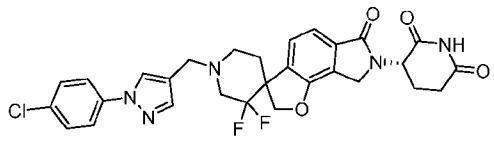
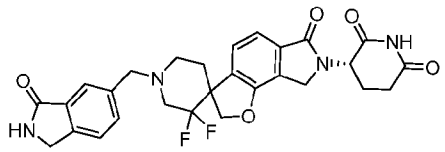
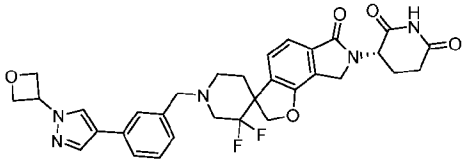
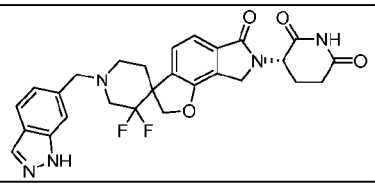
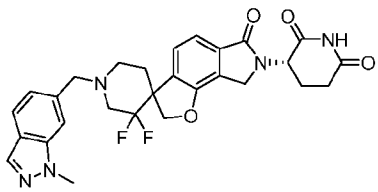
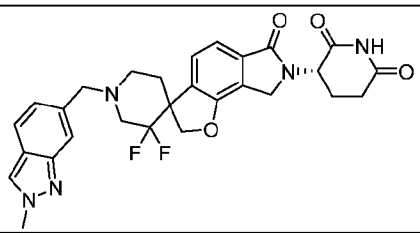
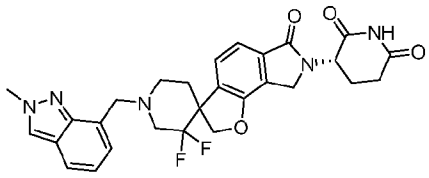
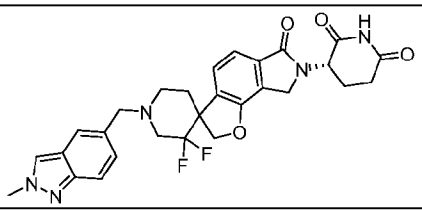
Table 2.

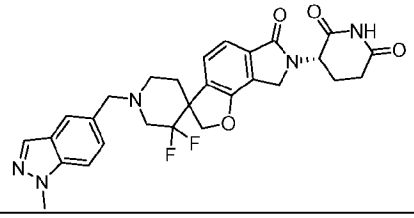
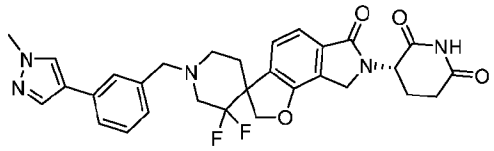
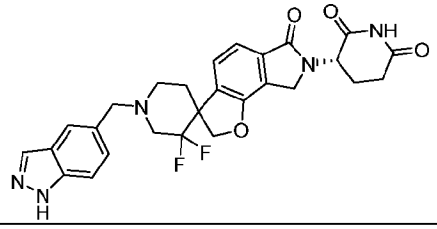
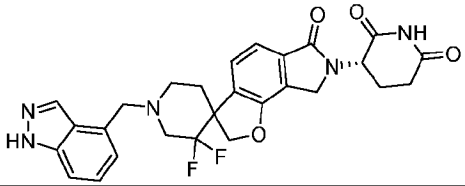
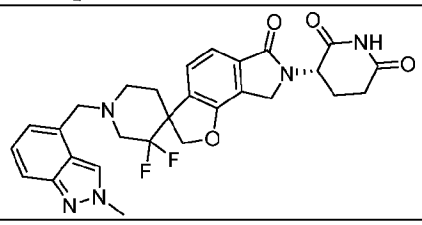
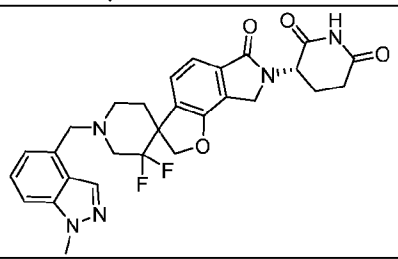
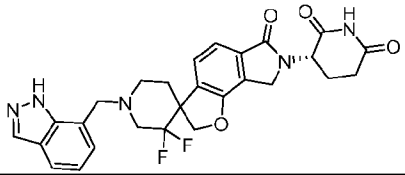
No.	Structure	Name
B1		(S)-3-(1'-((1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B2		(S)-3-(1'-((3-(4-chlorophenyl)isoxazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B3		(S)-3-(1'-((3-(4-chlorophenyl)isothiazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B4		(S)-3-(1'-((3-chloro-1-(4-chlorophenyl)-1H-pyrazol-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
B5		(S)-3-(1'-((1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-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
B6		(S)-3-(6-oxo-1'-((1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B7		(S)-3-(1'-((2-methyl-2H-indazol-6-yl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

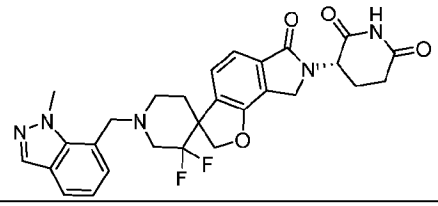
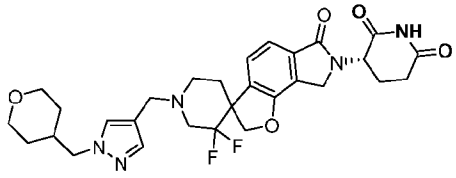
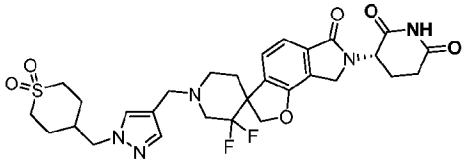
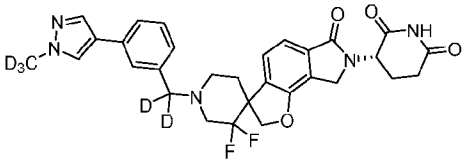
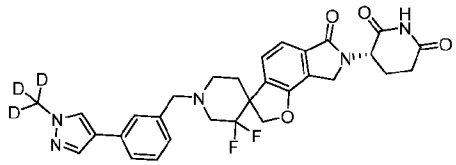
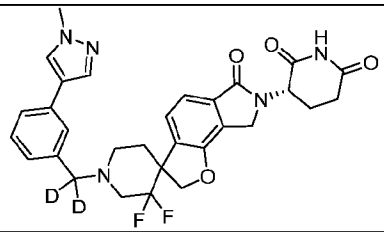
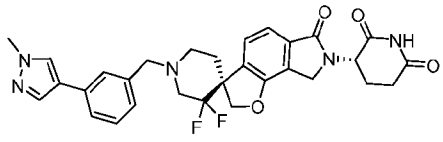
No.	Structure	Name
B8		(S)-3-(1'-((1-methyl-1H-indazol-6-yl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B9		(S)-3-(1'-((3-(1-(methyl-d3)-1H-pyrazol-4-yl)phenyl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B10		(S)-3-(1'-((3-(1-(difluoromethyl)-1H-pyrazol-4-yl)phenyl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B11		(S)-3-(1'-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B12		(S)-3-(1'-(3-(1-(methyl-d3)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B13		(S)-3-(1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl-2,2-d2)piperidine-2,6-dione
B14		(R)-3-(1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

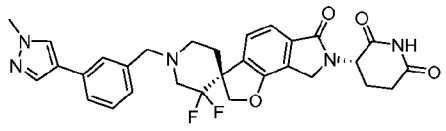
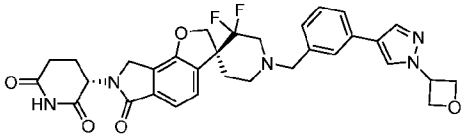
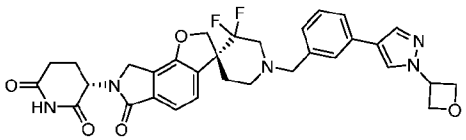
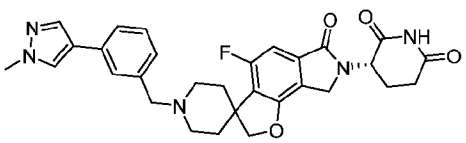
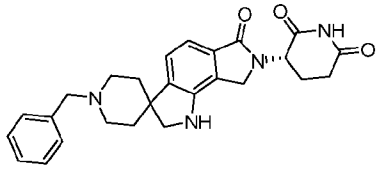
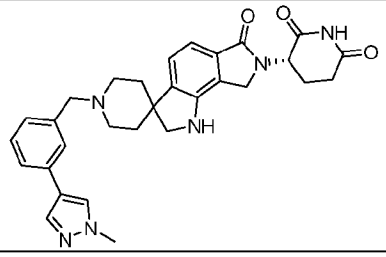
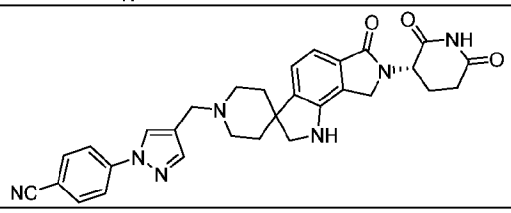
No.	Structure	Name
B15		(R)-3-(1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B16		(S)-3-(5-fluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B17		(S)-3-(1'-benzyl-5-chloro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B18		(S)-3-(1'-((1H-indazol-7-yl)methyl)-5-chloro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B19		(S)-7-(2,6-dioxopiperidin-3-yl)-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-5-carbonitrile
B20		(S)-3-(5-methyl-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B21		3-(3'-methyl-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

No.	Structure	Name
B22		3-(1'-benzyl-3'-hydroxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B23		3-(1'-benzyl-3'-fluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B24		3-(1'-((1H-indazol-7-yl)methyl)-3'-hydroxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B25		3-(1'-benzyl-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B26		3-(3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B27		4-(4-((7-((S)-2,6-dioxopiperidin-3-yl)-3',3'-difluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)-1H-pyrazol-1-yl)benzonitrile
B28		(3S)-3-(3',3'-difluoro-6-oxo-1'-((2-oxoindolin-5-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B29		(3S)-3-(1'-((1-((2-chlorophenyl)sulfonyl)-1H-pyrazol-4-yl)methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

No.	Structure	Name
B30		(3S)-3-(1'-((1-(4-chlorophenyl)-1H-pyrazol-4-yl)methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B31		(3S)-3-(3',3'-difluoro-6-oxo-1'-((3-oxoisoindolin-5-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B32		(3S)-3-(3',3'-difluoro-1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B33		(3S)-3-(1'-((1H-indazol-6-yl)methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B34		(3S)-3-(3',3'-difluoro-1'-((1-methyl-1H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B35		(3S)-3-(3',3'-difluoro-1'-((2-methyl-2H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B36		(3S)-3-(3',3'-difluoro-1'-((2-methyl-2H-indazol-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
B37		(3S)-3-(3',3'-difluoro-1'-((2-methyl-2H-indazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

No.	Structure	Name
B38		(3S)-3-(3',3'-difluoro-1'-((1-methyl-1H-indazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B39		(3S)-3-(3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B40		(3S)-3-(1'-((1H-indazol-5-yl)methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B41		(3S)-3-(1'-((1H-indazol-4-yl)methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B42		(3S)-3-(3',3'-difluoro-1'-((2-methyl-2H-indazol-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
B43		(3S)-3-(3',3'-difluoro-1'-((1-methyl-1H-indazol-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
B44		(3S)-3-(1'-((1H-indazol-7-yl)methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

No.	Structure	Name
B45		(3S)-3-(3',3'-difluoro-1'-((1-methyl-1H-indazol-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
B46		(3S)-3-(3',3'-difluoro-6-oxo-1'-((1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B47		(3S)-3-(1'-((1-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl)-1H-pyrazol-4-yl)methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B48		(3S)-3-(3',3'-difluoro-1'-((3-(1-(methyl-d3)-1H-pyrazol-4-yl)phenyl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B49		(3S)-3-(3',3'-difluoro-1'-(3-(1-(methyl-d3)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B50		(3S)-3-(3',3'-difluoro-1'-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B51		(S)-3-((S)-3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

No.	Structure	Name
B52		(S)-3-((R)-3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B53		(S)-3-((S)-3',3'-difluoro-1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B54		(S)-3-((R)-3',3'-difluoro-1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B55		(S)-3-(4-fluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
B56		(S)-3-(1-benzyl-6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)piperidine-2,6-dione
B57		(S)-3-(1-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)piperidine-2,6-dione
B58		(S)-4-(4-((7'-(2,6-dioxopiperidin-3-yl)-6'-oxo-1',6',7',8'-tetrahydro-2'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-1-yl)methyl)-1H-pyrazol-1-yl)benzonitrile

[0137] The compounds of the present disclosure may possess advantageous characteristics, as compared to known compounds, such as known IKZF2 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 may be measured according to methods commonly available in the art, such as methods exemplified herein.

[0138] 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.

[0139] In one embodiment, 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 another embodiment, 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 another embodiment, a compound of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a hydrate.

[0140] 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

[0141] 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.

[0142] In some embodiments, the compounds described herein possess acidic or basic groups and therefore 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.

[0143] 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.

[0144] 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.

[0145] 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 alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, magnesium, aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4}$ alkyl$)_4$, and the like.

[0146] 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

[0147] 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 invention.

[0148] 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 invention.

[0149] 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.

[0150] 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

[0151] 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."

[0152] 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 invention.

[0153] 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 invention.

[0154] 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

[0155] In some embodiments, compounds described herein exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein.

[0156] 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 invention. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Pharmaceutical Compositions

[0157] In certain embodiments, the compound described herein is administered as a pure chemical. In some embodiments, the compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[0158] 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.

[0159] 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.

[0160] 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.

[0161] 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.

Isotopic Species

[0162] In some aspects, the present disclosure provides a compound being an isotopic derivative (e.g., isotopically labeled compound) of any one of the compounds disclosed herein.

[0163] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1 or Table 2, or a pharmaceutically acceptable salt thereof.

[0164] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1 or Table 2.

[0165] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1, or a pharmaceutically acceptable salt thereof.

[0166] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1.

[0167] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 2, or a pharmaceutically acceptable salt thereof.

[0168] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 2.

[0169] It is understood that the isotopic derivative can be prepared using any of a variety of art-recognized techniques. For example, the isotopic derivative can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0170] In some embodiments, the isotopic derivative is a deuterium labeled compound.

[0171] In some embodiments, the isotopic derivative is a deuterium labeled compound of any one of the compounds of the Formulae disclosed herein.

[0172] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1 or Table 2, or a pharmaceutically acceptable salt thereof.

[0173] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1 or Table 2.

[0174] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1, or a pharmaceutically acceptable salt thereof.

[0175] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1.

[0176] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 2, or a pharmaceutically acceptable salt thereof.

[0177] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 2.

[0178] It is understood that the deuterium labeled compound comprises a deuterium atom having an abundance of deuterium that is substantially greater than the natural abundance of deuterium, which is 0.015%.

[0179] In some embodiments, the deuterium labeled compound has a deuterium enrichment factor for each deuterium atom of at least 3500 (52.5% deuterium incorporation at each deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). As used herein, the term "deuterium enrichment factor" means the ratio between the deuterium abundance and the natural abundance of a deuterium.

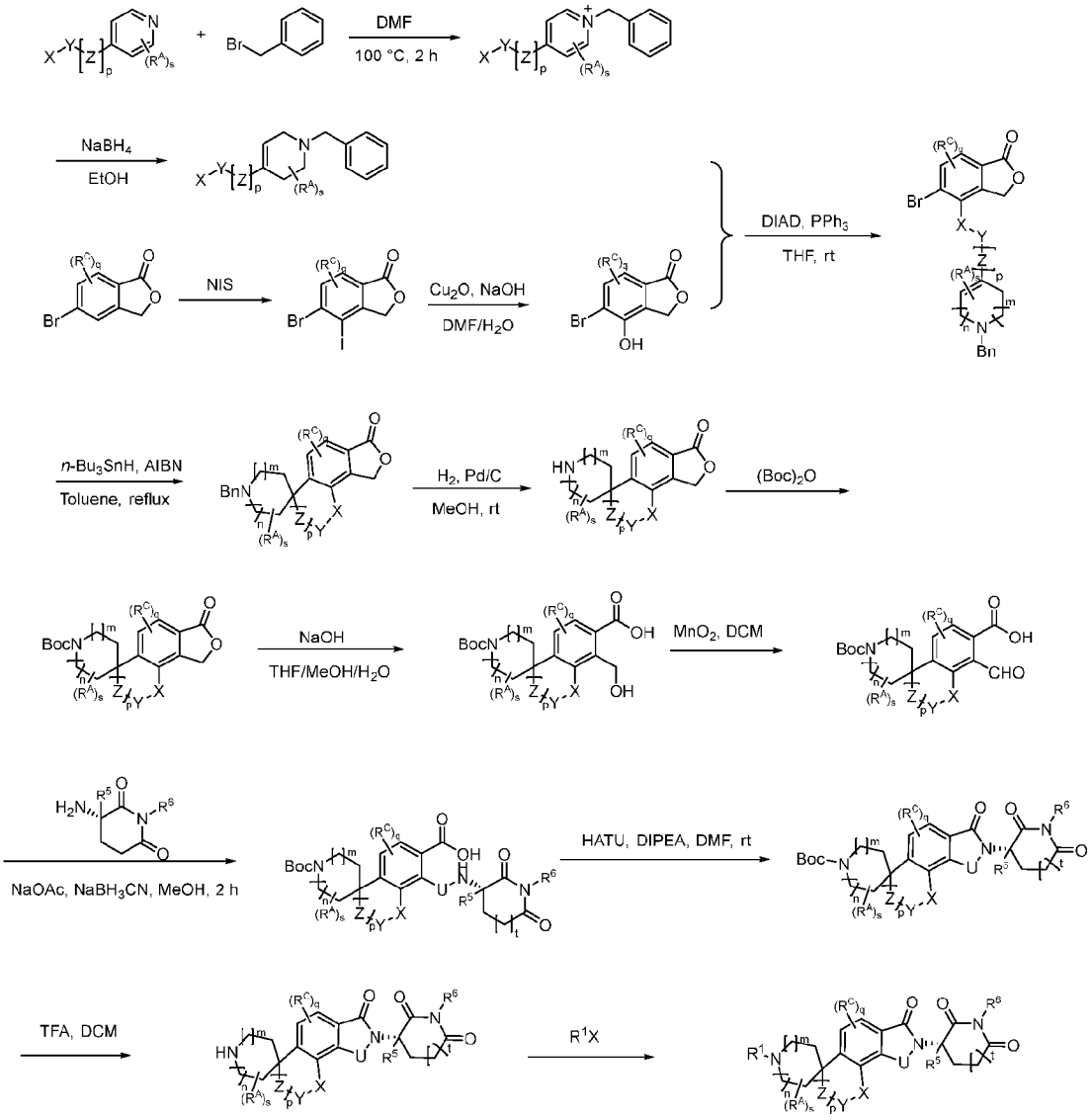
[0180] It is understood that the deuterium labeled compound can be prepared using any of a variety of art-recognized techniques. For example, the deuterium labeled compound can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting a deuterium labeled reagent for a non-deuterium labeled reagent.

[0181] A compound of the present disclosure or a pharmaceutically acceptable salt or solvate thereof that contains the aforementioned deuterium atom(s) is within the scope of the disclosure. Further, substitution with deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, e.g., increased *in vivo* half-life or reduced dosage requirements.

Preparation and Characterization of the Compounds

[0182] 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.*, in the Examples).

General Synthetic Scheme



[0183] 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).

[0184] 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).

[0185] 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.

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

[0186] 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.

Exemplary Biological Assays

[0187] The biological activities of the compounds of the present disclosure can be assessed with methods and assays known in the art.

Exemplary Cereblon Binding Assay

[0188] The binding to cereblon (CRBN) is determined using the Cereblon Binding Kit (Cisbio, #64BDCRBNPEG) following the manufacturer's instruction. Briefly, serially diluted compounds are incubated with GST-tagged wild-type human CRBN protein, XL665-labelled Thalidomide and Europium Cryptate labelled GST antibody . Time Resolved Fluorescence Resonance Energy Transfer (TR-FRET) measurements are acquired with, e.g., MARS data analysis software (BMG Labtech. The readings are normalized to the control (0.5%) and the IC_{50} is calculated by nonlinear regression (four parameters sigmoid fitted with variable slope) analysis using, e.g., the GraphPad Prism 8 software.

Exemplary Immunoblotting

[0189] Cells are maintained in the appropriate culture medium with 10% FBS at 37°C and an atmosphere of 5% CO_2.

[0190] Cells are lysed , resolved by SDS-PAGE , and transferred to a PVDF membrane (Millipore). Membranes are blocked, e.g., using Odyssey TBS Blocker Buffer (LI-COR). Secondary antibodies, e.g., IRDye 680RD and 800CW Dye-labeled are used. The washed membranes are scanned using e.g., an Odyssey CLx imager (LI-COR). The intensity of Western blot signaling is quantitated using the Odyssey software. Primary antibodies used include: Helios (D8W4X) XP® Rabbit mAb (Cell Signaling Technology, #42427) and GAPDH mouse monoclonal antibody (Santa Cruz Biotechnology, sc-47724).

Exemplary IKZF2 HiBiT assay

[0191] Degradation of IKZF2 protein is determined by IKZF2 HiBiT assay using the Jurkat-IKZF2-HiBiT (Promega) cell line. Briefly, cells are seeded in culture medium. Compounds are

serially diluted in culture medium, and certain volume of the diluted compounds is added to the appropriate well of the plate. After the addition of compounds, the cells are incubated. At the end of treatment, Nano-Glo HiBiT Lytic Detection Reagent (Promega) is added to each well, and then the plates are incubated at room temperature for a certain time period. The luminescent signal is measured using a CALRIOstar plate reader (BMG Labtech). The readings are normalized to the DMSO-treated cells and the IC_{50} is calculated by nonlinear regression (four parameters sigmoid fitted with variable slope, least squares fit, and no constraint) analysis using the GraphPad Prism 8 software.

Methods of Use

[0192] In certain aspects, the present disclosure provides methods of degrading a IKZF2 protein in a subject, comprising administering to the subject a compound disclosed herein.

[0193] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for degrading a IKZF2 protein in a subject.

[0194] In certain aspects, the present disclsoure provides compounds disclosed herein for use in degrading a IKZF2 protein in a subject.

[0195] 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).

[0196] 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).

[0197] 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.

[0198] 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.

[0199] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating or preventing a disease or disorderin a subject in need thereof.

[0200] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating a disease or disorderin a subject in need thereof.

[0201] In certain embodiments, the disease or disorder is an IKZF2-mediated disease or disorder.

[0202] In certain embodiments, the disease or disorder is a cancer.

[0203] In certain embodiments, the cancer includes, but is 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			

[0204] In certain embodiments, the cancer is a solid tumor. In certain embodiments, the cancer is 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	

[0205] In certain embodiments, the disease or disorder is T cell leukemia or T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, myeloid leukemia, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, or gastrointestinal stromal tumor (GIST).

[0206] In certain embodiments, the subject is a mammal.

[0207] In certain embodiments, the subject is a human.

Definitions

[0208] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

Chemical Definitions

[0209] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, Organic Chemistry, University Science Books, Sausalito, 1999; Smith and March, March's Advanced Organic Chemistry, 5th Edition, John Wiley & Sons,

Inc., New York, 2001; Larock, Comprehensive Organic Transformations, VCH Publishers, Inc., New York, 1989; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0210] 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).

[0211] The invention additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0212] 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.

[0213] 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 invention. 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.

[0214] "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 ($-CH_2CH(CH_3)_2$).

[0215] "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.

[0216] "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.

[0217] "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.

[0218] "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.

[0219] "Alkynylene" as used herein, refers to a alkynyl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of carbons is provided for a particular "alkynylene" group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. An "alkynylene" group may be substituted or unsubstituted with one or more substituents as described herein. Exemplary divalent alkynylene groups include, but are not limited to, substituted or unsubstituted ethynylene, substituted or unsubstituted propynylene, and the like.

[0220] 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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{1-7} alkyl"). In certain embodiments, a heteroalkyl group is a group having 1 to 6 carbon atoms and 1, 2, or 3 heteroatoms ("heteroC_{1-6} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms ("heteroC_{1-5} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and/or 2 heteroatoms ("heteroC_{1-4} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom ("heteroC_{1-3} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom ("heteroC_{1-2} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms ("heteroC_{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 heteroC_{1-10} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-10} alkyl.

[0221] The term "heteroalkenyl," as used herein, refers to an alkenyl group, as defined herein, which 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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{2-5} alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and lor 2 heteroatoms ("heteroC_{2-4} alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom ("heteroC_{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 ("heteroC_{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 heteroC_{2-10} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{2-10} alkenyl.

[0222] The term "heteroalkynyl," as used herein, refers to an alkynyl group, as defined herein, which comprises one or more (*e.g.,* 1, 2, 3, or 4) heteroatoms (*e.g.,* oxygen, sulfur, nitrogen, boron, silicon, phosphorus) wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms are inserted between a carbon atom and the parent molecule, *i.e.,* between the point of attachment. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms ("heteroC_{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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{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 ("heteroC_{2-5} alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and lor 2 heteroatoms ("heteroC_{2-4} alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom ("heteroC_{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 ("heteroC_{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 heteroC_{2-10} alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC_{2-10} alkynyl.

[0223] 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.

[0224] "Aryl" refers to a radical of a monocyclic or polycyclic (e.g., bicyclic or tricyclic) 4n+2 aromatic ring system (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; e.g., phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; e.g., anthracyl).

[0225] 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.

[0226] "Arylene" as used herein, refers to an aryl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of carbons is provided for a particular

"arylene" group, it is understood that the range or number refers to the range or number of carbons in the aryl group. An "arylene" group may be substituted or unsubstituted with one or more substituents as described herein.

[0227] "Heteroaryl" refers to a radical of a 5- to 14-membered monocyclic or polycyclic 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1-8 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5- to 14-membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings.

[0228] "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).

[0229] 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.

[0230] 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.

[0231] "Heteroarylene" as used herein, refers to a heteroaryl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of ring members is provided for a particular "heteroarylene" group, it is understood that the range or number refers to the number of ring members in the heteroaryl group. A "heteroarylene" group may be substituted or unsubstituted with one or more substituents as described herein.

[0232] "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.

[0233] 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.

[0234] 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.

[0235] "Fused carbocyclyl" or "fused carbocycle" refers to ring systems wherein the carbocyclyl group, as defined above, is fused with, i.e., share two common atoms (as such, share one common bond), 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.

[0236] "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 embedded. In such instances, the number of carbons designates the total number of carbons of the carbocyclyl rings in which the spiro structure is embedded. When substitution is indicated, unless otherwise specified, substitution can occur on the carbocyclyl rings in which the spiro structure is embedded.

[0237] "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 two 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 embedded. In such instances, the number of carbons designates the total number of carbons of the carbocyclyl rings in which the bridged structure is embedded. When substitution is indicated, unless otherwise specified, substitution can occur on any of the carbocyclyl rings in which the bridged structure is embedded.

[0238] "Carbocyclylene" as used herein, refers to a carbocyclyl group wherein two hydrogens are removed to provide a divalent radical. The divalent radical may be present on different atoms or the same atom of the carbocyclylene group. When a range or number of carbons is provided for a particular "carbocyclyl" group, it is understood that the range or number refers

to the range or number of carbons in the carbocyclyl group. A "carbocyclyl" group may be substituted or unsubstituted with one or more substituents as described herein.

[0239] "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.

[0240] 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.

[0241] 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.

[0242] "Fused heterocyclyl" or "fused heterocycle" refers to ring systems wherein the heterocyclyl group, as defined above, is fused with, i.e., share two common atoms (as such, 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 ring members 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.

[0243] "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 embedded. 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 embedded. When substitution is indicated, unless otherwise specified, substitution can occur on any of the heterocyclyl or carbocyclyl rings in which the spiro structure is embedded.

[0244] "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 two 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 embedded. 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 embedded. When substitution is indicated, unless otherwise specified, substitution can occur on any of the heterocyclyl or carbocyclyl rings in which the bridged structure is embedded.

[0245] "Heterocyclylene" as used herein, refers to a heterocyclyl group wherein two hydrogens are removed to provide a divalent radical. The divalent radical may be present on different atoms or the same atom of the heterocyclylene group. When a range or number of ring members is provided for a particular "heterocyclylene" group, it is understood that the range or number refers to the number of ring members in the heterocyclylene group. A "heterocyclylene" group may be substituted or unsubstituted with one or more substituents as described herein.

[0246] "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.

[0247] "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.

[0248] "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.

[0249] "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.

[0250] "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.

[0251] 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)).

[0252] 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)).

[0253] Common types of thiol-protecting groups include but not limited to sulfide (*e.g.,* p-methylbenzyl (Meb), *t*-butyl, acetamidomethyl (Acm), and triphenylmethyl (Trityl)).

[0254] 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.

[0255] 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

[0256] "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.

[0257] "Pharmaceutically acceptable salt" refers to a salt of a compound of the invention 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.

[0258] "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 invention 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.

[0259] 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.

[0260] 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.

[0261] "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).

[0262] 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.

[0263] "Treating" or "treatment" or "therapeutic treatment" of any disease or disorder refers, in one embodiment, 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 another embodiment, "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, "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.

[0264] 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."

[0265] 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".

[0266] "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 π 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.

[0267] 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.

[0268] 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.

[0269] 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.

[0270] 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.

[0271] 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.

[0272] 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.

[0273] 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.

[0274] 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 one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[0275] 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.

[0276] 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 one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including

elements other than A); in yet another embodiment, 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).

[0277] 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.

[0278] 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.

[0279] 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.

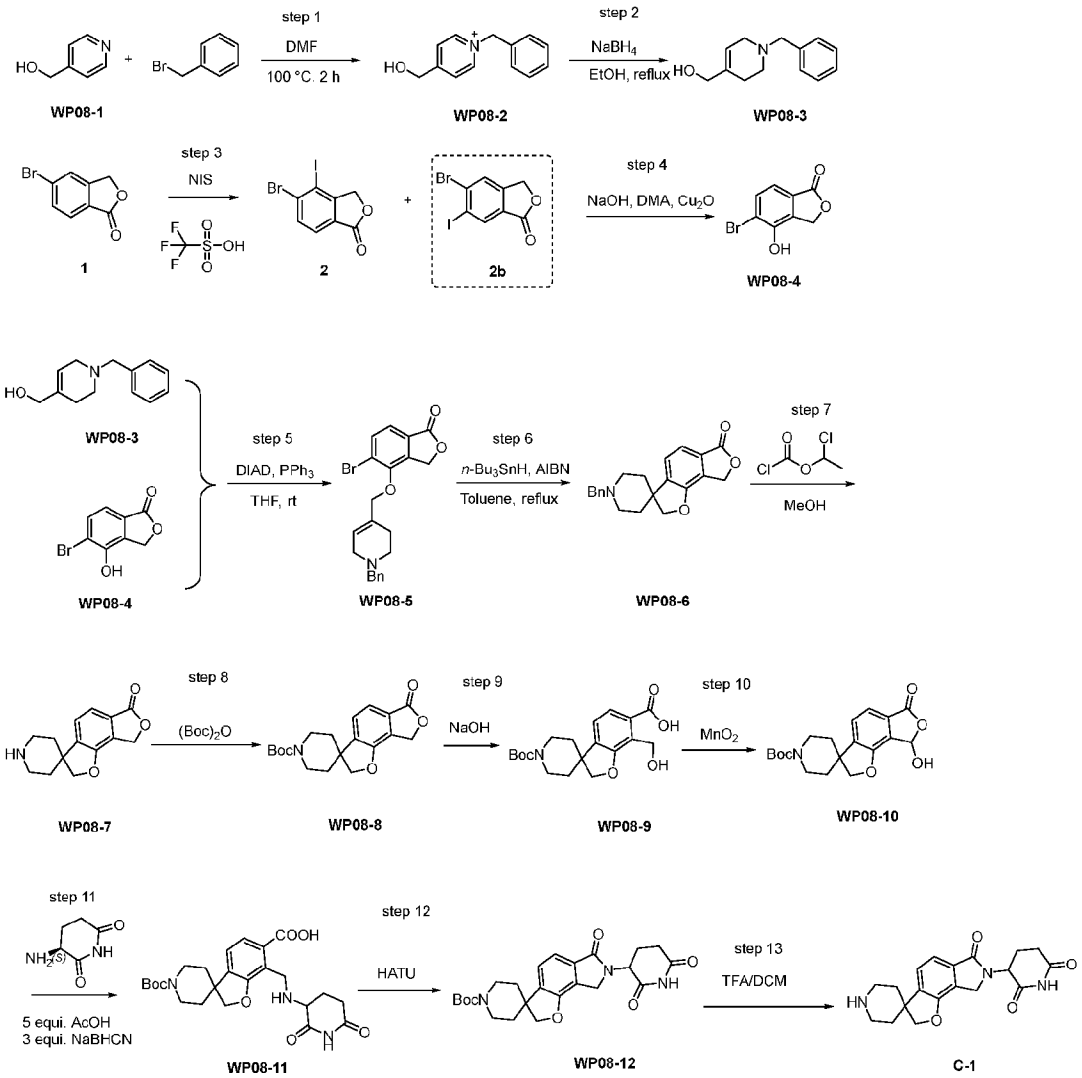
EXAMPLES

[0280] 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.

I. Synthetic Routes and Procedures

3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione(C-1)



Step 1-2:

[0281] To a solution of pyridin-4-ylmethanol (**WP08-1**, 100 g, 916 mmol, 1.0 eq.) in DMF (400 mL) was added BnBr (172 g, 1.0 mol, 1.1 eq.). The mixture was allowed to heat to 100°C and stirred 3 h. TLC showed no starting material remained and a new spot formed. The residue was dissolved in EtOH (1500 mL), then 45 g of sodium borohydride (1.19 mol, 1.3 eq.) was added portionwise at 0°C. The mixture was continued to stir at 0°C for 1 h and then at reflux for 2 h. The solvent was evaporated under reduced pressure, then water was added, and the

mixture was extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatograph (DCM:MeOH = 100:0-30:1) to afford 107 g of product **WP08-3** (Viscous oil, 2 steps, yield 80%).

[0282] LC/MS (ESI) m/z: 204.14; ^{1}H NMR (400 MHz, $CDCl_3$): 7.25-7.41 (m, 5H), 5.59-5.66 (m, 1H), 4.01 (s, 2H), 3.60 (s, 2H), 2.95-3.02 (m, 2H), 2.61 (t, J = 5.8 Hz, 2H), 2.36 (s,br, 1H), 2.10-2.21 (m, 2H).

Step 3:

[0283] To a solution of 5-Bromo-3H-isobenzofuran-1-one (**1**) (100 g, 1 eq.) in trifluoromethanesulfonic acid (1000 g, 10 eq) was added NIS (125 g, 1.2 eq.) at 0 °C in portions. The mixture was allowed to warm to room temperature and stirred overnight. TLC showed no starting material remained and two new spots formed. The reaction mixture was poured into ice-water and yellow solid precipitated. The mixture was filtered and the filter cake was washed with ice cold water. The filter cake was dried and obtained as a yellow solid (100 g, yield 62%), to be a mixture of product **2** (top spot on TLC) and product **2b** (bottom spot on TLC, which was not further reacted in next step).

[0284] LC/MS (ESI) m/z: 337.84; ^{1}H NMR (400 MHz, $CDCl_3$): 7.83 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 5.10 (s, 2H).

Step 4:

[0285] To a mixture of compound **2** (100 g, 1 eq.), sodium hydroxide (57.5 g, 5 eq.) in water (1000 mL, 1.5 M) and N,N-dimethylacetamide (600 mL) was added cuprous oxide (8.5 g, 0.2 eq.). The reaction mixture was heated to 80 °C and stirred for 12 h. TLC showed the compound **2** (top spot on TLC) was completely consumed. The reaction mixture was poured into water (1000 mL) and treated with solid K_2CO_3 until pH 8–9, and extracted with EA. The aqueous layer neutralized using 1 N hydrochloride solution and extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate and evaporated. The crude product was purified by silica gel column chromatography to give compound **WP08-4** was obtained as a yellow solid (42 g, 39% yield).

[0286] LC/MS (ESI) m/z: 228.94; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 5.35 (s, 2H).

Step 5:

[0287] To a solution of compound **WP08-4** (20 g, 1.0 eq.) in 200 mL of THF, compound **WP08-3** (23.1 g, 1.3 eq.) and PPh_3 (34.4 g, 1.55 eq.) was added. The reaction mixture was cooled to 0°C and DIAD (27.1 mL, 1.55 eq.) was added dropwise. The resulting mixture was then stirred overnight at room temperature. The solvent was evaporated at reduced pressure

and the crude product was purified by silica gel column chromatography using 0-100% EtOAc/hexane. The desired product **WP08-5** was obtained as a yellow foam (17.7 g, yield 49%).

[0288] LC/MS (ESI) m/z: 414.0.

Step 6:

[0289] To a solution of **WP08-5** (14.8 g, 35.7 mmol, 1.0 eq.) in toluene (150 mL) was added n-Bu_3SnH (41.6 g, 142.9 mmol, 4.0 eq.) and AIBN (0.6 g, 3.57 mmol, 0.1 eq.). The mixture was heated to reflux and stirred overnight. TLC (PE:EA = 1:1) showed no starting material remained and new spots formed. The reaction mixture was poured into saturated aq. KF solution (100 mL) and stirred overnight. Then, the reaction mixture was extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate. The crude product was purified by silica gel column chromatography (DCM:MeOH = 50:1) to give compound **WP08-6** was obtained as a white solid (7.1 g, 60% yield).

[0290] LC/MS (ESI) m/z: 336.15.

Step 7-8:

[0291] To a solution of **WP08-6** (10 g, 29.8 mmol, 1.0 eq.) in DCE (100 mL) was added α-chloroethyl chloroformate (ACE-Cl, 1.0 eq.) at 0 °C and then refluxing the mixture for 1 h. The intermediate ACE-piperidine formed and is usually de-ACEylated directly to **WP08-7** by evaporating the reaction mixture in vacuo and then heating the residue in MeOH. The residue was dissolved in THF (100 mL), then 4.5 g of triethylamine (44.7 mmol, 1.5 eq.) and Boc_2O (38.7 mmol, 1.3 eq.) was added. The mixture was continued to stir for 3 h at room temperature. The solvent was evaporated under reduced pressure, then water was added, and the mixture was extracted with EA. The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatograph to afford 6.0 g of product **WP08-8** (2 steps, yield 60%).

[0292] LC/MS (ESI) m/z: 346.16.

Step 9:

[0293] To a solution of compound **WP08-8** (15 g, 1 eq.) in tetrahydrofuran (100 mL) and water (100 mL) was added sodium hydroxide (8.7 g, 5 eq). The mixture was stirred at 20 °C for 16 h. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The mixture was adjusted to pH = 5-6 with aq. hydrochloric acid (1 M) and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The crude material was not further purified and used as crude for the next step.

[0294] LC/MS (ESI) m/z: 364.17.

Step 10:

[0295] To a solution of compound **WP08-9** (15 g, crude, 1 eq.) in dichloromethane (300 mL) was added manganese dioxide (20 eq.). The mixture was stirred at 20 °C for about 1 h. TLC showed reaction was complete. The mixture was diluted with dichloromethane and filtered through a pad of Celite. The filtrate was concentrated in vacuum. The crude product was purified by silica gel column chromatography (DCM: MeOH = 10:1). The desired compound **WP08-10** was obtained as yellow solid. (8 g, 2 steps, 60%).

[0296] LC/MS (ESI) m/z: 362.15.

Step 11:

[0297] To a mixture of compound **WP08-10** (3 g, 1.0 eq.) in methanol (20 mL) and dichloromethane (20 mL) was added 3-aminopiperidine-2,6-dione (4.0 g, 3 eq., TFA salt), AcONa (3.08 g, 6.0 eq.) and AcOH (5.1 mL, 10.0 eq.). The mixture was stirred at 25 °C for 2 h, then sodium cyanoborohydride (1.57 g, 3.0 eq.) was added and the mixture was further stirred for 30 min. LCMS showed the reaction was complete. Next, the reaction mixture was quenched with water and concentrated under reduced pressure to give a residue which was redissolved in acetonitrile and water (1:1, 30 mL). The solution was mixed well at beginning. After standing at 0-5 °C overnight, the mixture was filtered, and the filter cake was washed with acetonitrile and water (1:1) and vacuum dried to afford the crude product **WP08-11** as a solid (900 mg, yield 60%).

[0298] LC/MS (ESI) m/z: 474.22.

Step 12:

[0299] To a solution of compound **WP08-11** (900 mg 1.0 equiv) in DMF (15 mL) was added HATU (795 mg, 1.1 equiv) and DIPEA (0.72 mL, 3.0 equiv), and the reaction was stirred at rt for 30 min. UPLC-MS indicated a new main peak with desired MS formed, then quenched with water and the mixture was extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate. The target compound **WP08-12** was obtained as a brown solid (675 mg, 75% yield).

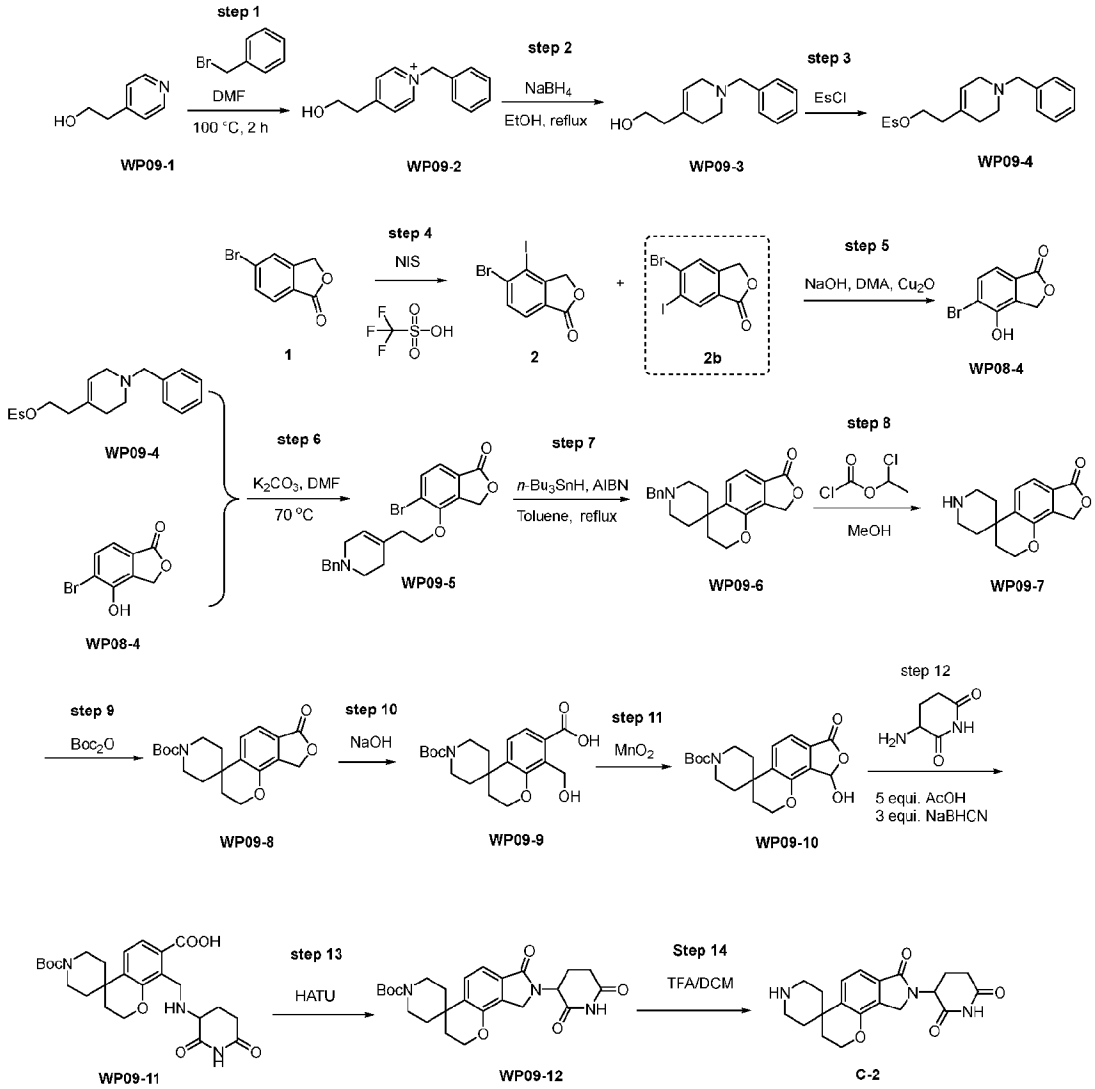
[0300] LC/MS (ESI) m/z: 456.21. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.28 (s, 1H), 5.23 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.55 (d, *J* = 1.4 Hz, 2H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.32 (d, *J* = 16.0 Hz, 1H), 4.15 (s, 2H), 3.01 – 2.77 (m, 4H), 2.38 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.29 – 2.17 (m, 1H), 1.92 (t, *J* = 12.5 Hz, 2H), 1.83 – 1.72 (m, 2H), 1.52 (s, 9H).

Step 13:

[0301] Compound **WP08-12** was treated with TFA in DCM at room temperature to de-protect the N-Boc group to provide the cereblon ligand **C-1**.

[0302] LC/MS (ESI) m/z: 355.1.

3-(7'-oxo-2',3',7',9'-tetrahydro-8'H-spiro[piperidine-4,4'-pyrano[2,3-e]isoindol]-8'-yl)piperidine-2,6-dione (C-2):



Step 1-2:

[0303] To a solution of 2-(pyridin-4-yl)ethan-1-ol (**WP09-1**, 10 g, 91.6 mmol, 1.0 eq.) in DMF (40 mL) was added BnBr (15.3 g, 108 mmol, 1.1 eq.). The mixture was allowed to heat to 100°C and stirred 3 h. TLC showed no starting material remained and a new spot formed. The residue was dissolved in EtOH (150 mL), then 4.0 g of sodium borohydride (119.1 mmol, 1.3 eq.) was added portionwise at 0°C. The mixture was continued to stir at 0°C for 1 h and then at reflux

for 2 h. The solvent was evaporated under reduced pressure, then water was added, and the mixture was extracted with EA. The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatograph (DCM:MeOH = 100:0-30:1) to afford 10 g of product **WP09-3** (Viscous oil, 2 steps, yield 56%).

[0304] LC-MS: 218 $[M+H]^+$.

Step 3:

[0305] To a solution of compound **WP09-3** (10 g, 1 eq.) in DCM (200.0 mL) was added DMAP (0.1 eq.) and TEA (2 eq.) at 0 °C. Then EsCl (1.5 eq.) was slowly added into and the mixture was stirred at R.T. for 1 h. The reaction was partitioned between EtOAc and water. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatograph to give compound **WP09-4** as a yellow solid (10 g, yield 70%).

[0306] LC-MS: 310 $[M+H]^+$.

Step 4:

[0307] To a solution of 5-Bromo-3H-isobenzofuran-1-one (**1**) (10 g, 1 eq.) in trifluoromethanesulfonic acid (100 g, 10 V) was added NIS (12.5 g, 1.2 eq.) at 0 °C in portions. The mixture was allowed to warm to room temperature and stirred overnight. TLC showed no starting material remained and two new spots formed. The reaction mixture was poured into ice-water and yellow solid precipitated. The mixture was filtered and the filter cake was washed with ice cold water. The filter cake was dried and obtained as a yellow solid (10 g, yield 62%), to be a mixture of product **2** (top spot on TLC) and product **2b** (bottom spot on TLC, which was not further reacted in next step).

Step 5:

[0308] To a mixture of compound **2** (10 g, 1 eq.), sodium hydroxide (5.75 g, 5 eq.) in water (100 mL, 1.5 M) and N,N-dimethylacetamide (60 mL) was added cuprous oxide (0.85 g, 0.2 eq.). The reaction mixture was heated to 80 °C and stirred for 12 h. TLC showed the compound **2** (top spot on TLC) was completely consumed. The reaction mixture was poured into water (100 mL) and treated with solid K_2CO_3 until pH 8–9, and extracted with EA. The aqueous layer neutralized using 1 N hydrochloride solution and extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate and evaporated. The crude product was purified by silica gel column chromatography to give compound **WP08-4** was obtained as a yellow solid (4.2 g, 39% yield).

[0309] LC-MS: 229/231 $[M+H]^+$.

Step 6:

[0310] To a solution of compound **WP08-4** (10 g, 1.0 eq.) in 100 mL of DMF, compound **WP09-4** (16.2 g, 1.2 eq.) and K_2CO_3 (1.6 eq.) was added. The reaction mixture was heated to 70°C and stirred overnight. The reaction mixture was poured into ice-water and extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate. The solvent was evaporated at reduced pressure and the crude product was purified by silica gel column chromatography using 0-100% EtOAc/hexane. The desired product **WP09-5** was obtained as a yellow foam (11 g, yield 60%).

[0311] LC-MS: 428/430 $[M+H]^+$.

Step 7:

[0312] To a solution of **WP09-5** (5 g, 1.0 eq.) in toluene (50 mL) was added n-Bu_3SnH (13.6 g, 4.0 eq.) and AIBN (0.4 g, 0.1 eq.). The mixture was heated to reflux and stirred overnight. TLC (PE:EA = 1:1) showed no starting material remained and new spots formed. The reaction mixture was poured into saturated aq. KF solution (100 mL) and stirred overnight. Then, the reaction mixture was extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate. The crude product was purified by silica gel column chromatography (DCM:MeOH = 50:1) to give compound **WP09-6** was obtained as a white solid (2 g, 50% yield).

[0313] LC-MS: 350 $[M+H]^+$.

Step 8-9:

[0314] To a solution of **WP09-6** (3.0 g, 1.0 eq.) in DCE (100 mL) was added α-chloroethyl chloroformate (ACE-Cl, 1.2 eq.) at 0 °C and then refluxing the mixture for 15 h. The intermediate ACE-piperidine formed and is usually de*ACE*ylated directly to **WP09-7** by evaporating the reaction mixture in vacuo and then heating the residue in MeOH. The residue was dissolved in THF (100 mL), then trimethylamine (3.0 eq.) and Boc_2O (1.3 eq.) was added. The mixture was continued to stir for 3 h at room temperature. The solvent was evaporated under reduced pressure, then water was added, and the mixture was extracted with EA. The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatograph to afford **WP09-8** (1.5 g, 2 steps, yield 50%).

[0315] LC-MS: 360 $[M+H]^+$. ^1H NMR (600 MHz, Chloroform-d) δ 7.47 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 5.24 (s, 2H), 4.16 (t, J = 6.7 Hz, 2H), 3.88 (m, 2H), 3.51 (m, 2H), 2.52 (t, J = 6.8 Hz, 2H), 2.13 (m, 2H), 1.61 (m, 2H), 1.46 (s, 9H).

Step 10:

[0316] To a solution of compound **WP09-8** (2 g, 1 eq.) in tetrahydrofuran (10 mL) and water (10 mL) was added sodium hydroxide (1.2 g, 5 eq.). The mixture was stirred at 20 °C for 16 h.

TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The mixture was adjusted to pH = 5-6 with aq. hydrochloric acid (1 M) and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The crude material was not further purified and used as crude for the next step.

Step 11:

[0317] To a solution of compound **WP09-9** (2 g, crude, 1 eq.) in dichloromethane (30 mL) was added manganese dioxide (20 eq.). The mixture was stirred at 20 °C for about 1 h. TLC showed reaction was complete. The mixture was diluted with dichloromethane and filtered through a pad of Celite. The filtrate was concentrated in vacuum. The crude product was purified by silica gel column chromatography (DCM: MeOH = 10:1). The desired compound **WP09-10** was obtained as yellow solid. (1.2 g, 2 steps, 60%).

[0318] LC-MS: 376 $[M+H]^+$.

Step 12:

[0319] To a mixture of compound **WP09-10** (532 mg, 1.0 eq.) in methanol (5 mL) and dichloromethane (5 mL) was added 3-aminopiperidine-2,6-dione (698 mg, 3 eq., HCl salt), AcONa (698 mg, 6.0 eq.) and AcOH (0.85 mL, 10.0 eq.). The mixture was stirred at 25 °C for 1 h, then sodium cyanoborohydride (268 mg, 3.0 eq.) was added and the mixture was further stirred for 30 min. LCMS showed the reaction was complete. Next, the reaction mixture was quenched with water and concentrated under reduced pressure to give a residue which was purified by pre-HPLC (20% ~ 50% ACN, neutral). The desired product **WP09-11** as a solid (415 mg, yield 60%) after lyophilization.

Step 13:

[0320] To a solution of compound **WP09-11** (415 mg 1.0 equiv) in DMF (5 mL) was added HATU (421 mg, 1.3 equiv) and DIPEA (0.47 mL, 3.0 equiv), and the reaction was stirred at rt for 30 min. UPLC-MS indicated a new main peak with desired MS formed, then quenched with water and the mixture was extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate. The desired compound **WP09-12** was obtained as a brown solid (300 mg, 75% yield).

[0321] LC-MS: 470 $[M+H]^+$.

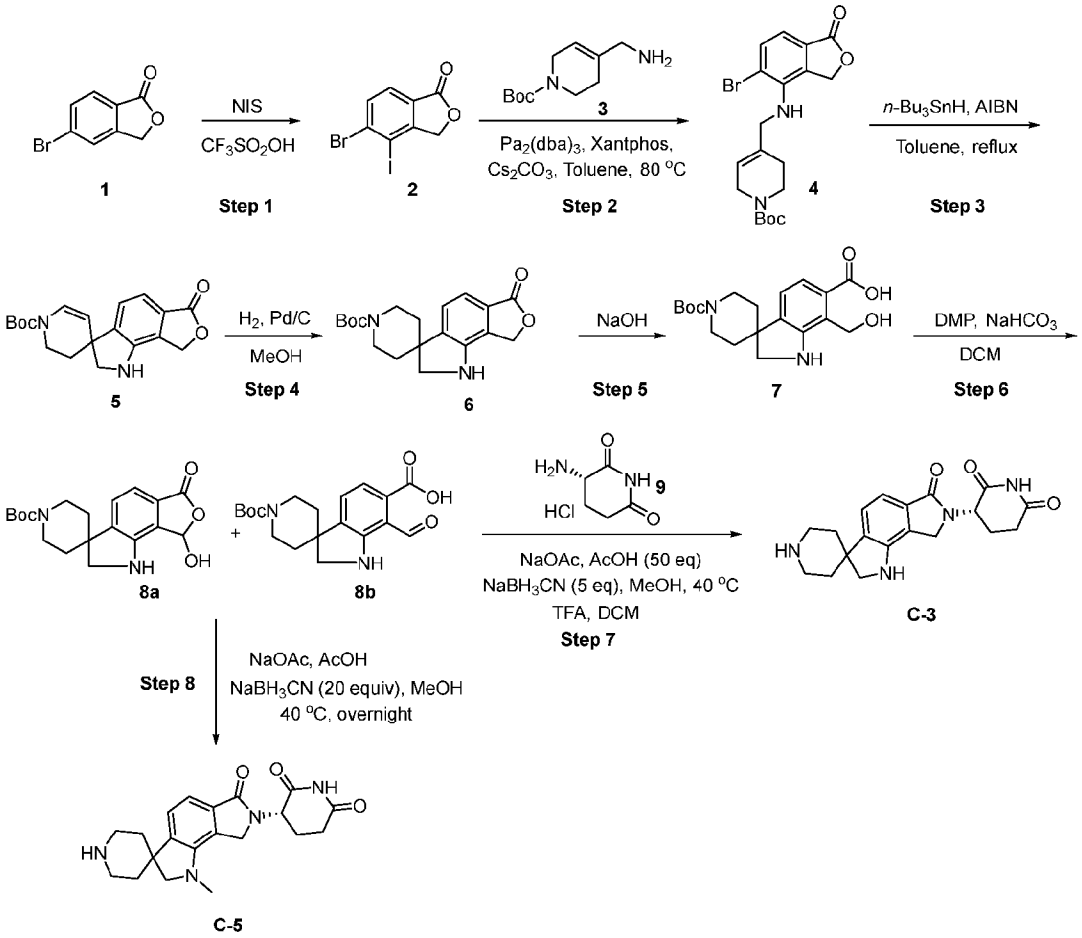
Step 14:

[0322] Compound **WP09-12** was treated with TFA in DCM at room temperature to de-protect the N-Boc group to provide the cereblon ligand **C-2.**

[0323] LC/MS (ESI) m/z: 369.2.

(S)-3-(6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)piperidine-2,6-dione (C-3); and

(S)-3-(1'-methyl-6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)piperidine-2,6-dione (C-5)



Step 1:

[0324] To a solution of 5-Bromo-3H-isobenzofuran-1-one (**1**) (10 g, 1 eq.) in trifluoromethanesulfonic acid (100 g, 10 V) was added NIS (12.5 g, 1.2 eq.) at 0 °C in portions. The mixture was allowed to warm to room temperature and stirred overnight. TLC showed no starting material remained and two new spots formed. The reaction mixture was poured into ice-water and yellow solid precipitated. The mixture was filtered and the filter cake was washed with ice cold water. The filter cake was dried and obtained as a yellow solid (10 g, yield 62%), to be a mixture of product **2** (top spot on TLC) and product **2b** (bottom spot on TLC, which was not further reacted in next step).

Step 2:

[0325] Compound **3** was made according to the procedure reported (*Bioorg. Med. Chem. Lett.*

2016, *26*, 228–234). To a flask containing compound **2** (500 mg, 1.0 eq.), compound **3** (377 mg, 1.2 eq.), $Pd_2(dba)_3$ (136 mg, 0.1 eq.), Xantphos (257 mg, 0.3 eq.) and Cs_2CO_3 (1447 mg, 3.0 eq.) was added Toluene (15 mL). The reaction was evacuated and backfilled with N_2 three times. The reaction was stirred at 80 °C for 6 h and then was allowed to cool to room temperature and filtered. The filtrate was evaporated, and the residue was purified by silica gel chromatography (0-25% ethyl acetate in hexane) to afford product **4** as a light yellow powder 316 mg (yiled = 51%).

[0326] LC-MS: 323.14 [M+H]+. 1H NMR (400 MHz, Chloroform-d) δ 7.61 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 5.64 – 5.53 (m, 1H), 5.36 (s, 2H), 3.93 – 3.79 (m, 4H), 3.53 (t, J = 5.7 Hz, 2H), 2.17 – 2.05 (m, 2H), 1.46 (s, 9H).

Step 3 and step 4:

[0327] To a solution of compound **4** (300 mg, 1.0 eq.) and AIBN (35 mg, 0.3 eq.) in Toluene (10 mL) was added Bu_3SnH (954 uL, 5.0 eq.). The reaction was stirred at 110 °C in a sealed tube for 24 h. Then cooled to room temperature, quenched with saturated aq. KF solution (20 mL) and kept the mixture stirring overnight. The result mixture was extracted with ethyl acetate (3 times). The combined organic layers were washed with brine (3 times), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude mixture. The mixture was purified by silica gel chromatography (0-30% ethyl acetate in hexane) to afford the crude product **5** as a light-yellow oil (90 mg).

[0328] LC-MS: 343.37 $[M+H]^+$.

[0329] To a solution of compound **5** (90 mg) in MeOH (5 mL) was added Pd/C (90 mg). The reaction was evacuated and backfilled with H_2 and stirred at room temperature under H_2 atmosphere for 6 h. Then filtered through celite and the filtration was concentrated under reduced pressure to give the cude product, which is purified by silica gel chromatography (0-50% ethyl acetate in hexane) to afford the compound **6** as a white solid (50 mg, 20% yield for steps **3** and **4**).

[0330] LC-MS: 345.22 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 5.20 (s, 2H), 4.19 – 4.04 (m, 2H), 3.67 (s, 2H), 3.00 – 2.77 (m, 2H), 1.91 – 1.68 (m, 4H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.42, 154.87, 143.02, 142.81, 128.22, 126.10, 123.66, 117.49, 79.98, 67.97, 56.18, 44.96, 40.85, 35.64, 28.54.

Step 5:

[0331] To a solution of **6** (48 mg, 1.0 equiv) in THF/MeOH/H2O (2 mL/2 mL/1 mL) was added NaOH (111 mg, 20 equiv). The reaction was stirred at rt overnight, then concentrated to remove most of the THF/MeOH. The residue was diluted with 1 mL water, followed by

neutralization with 2 N aq HCl to PH 4-6, then extracted with EA (5 mL, 6 times). The combined organic layer was washed with brine, filtered, dried with Na_2SO_4, and concentrated under reduced pressure to give the crude product **7** as a light-yellow oil 50 mg, which was directly used in the next step.

[0332] LC-MS: 363.28 $[M+H]^+$.

Step 6:

[0333] To a solution of **7** (40 mg, 1.0 equiv) in DCM (5 mL) was added $NaHCO_3$ (28 mg, 3.0 eq.), followed by add DMP (47 mg, 1.0 equiv) potionwise. 10 min Later, the reaction mixture was diluted with DCM and washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford the crude product **8** as a yellow oil 40 mg, which was directly used in the next step.

LC-MS: 361.27 $[M+H]^+$.

Step 7:

[0334] To a solution of **9** (73 mg, 4.0 equiv) and NaOAc (28 mg, 4 equiv) in MeOH (4 mL) was added **8** (40 mg, 1.0 equiv) and AcOH (317 uL, 50 eq.). 15 min Later, $NaBH_3CN$ (34.5 mg, 5.0 eq.) was added, and the resulted mixture was stirred at 40 °C for 3 h. The reaction mixture was concentrated to remove some MeOH, and then purified by pre-HPLC to give the Boc-protected **C-3**, which is further treated with TFA and concentrated to remove TFA. The final compound **C-3** was obtained as a white solid 10 mg.

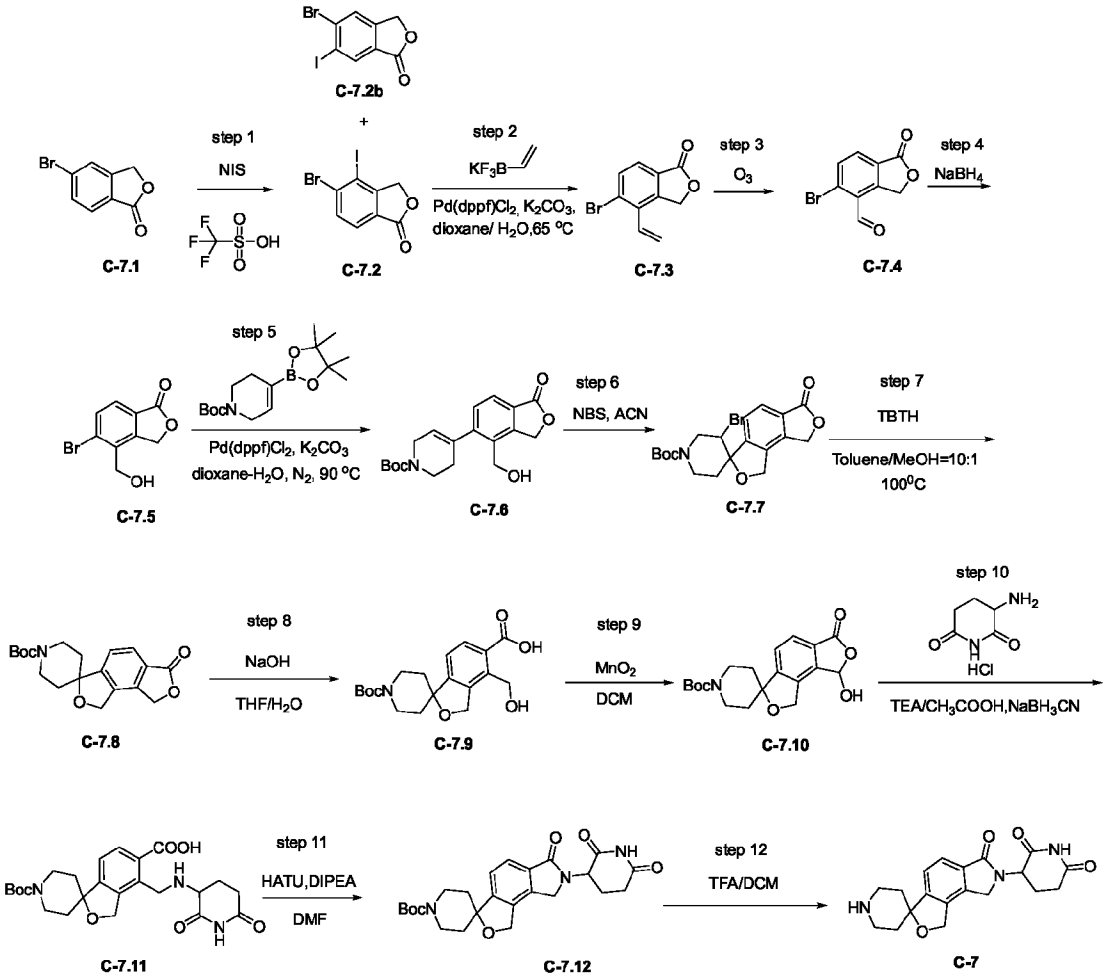
[0335] LC-MS: 423.16 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.28 – 7.17 (m, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.39 – 4.23 (m, 2H), 3.67 (s, 2H), 3.51 – 3.39 (m, 2H), 3.25 – 3.12 (m, 2H), 2.98 – 2.84 (m, 1H), 2.84 – 2.72 (m, 1H), 2.56 – 2.39 (m, 1H), 2.23 – 1.96 (m, 5H).

Step 8:

[0336] To a solution of **9** (18 mg, 4.0 equiv) and NaOAc (6.9 mg, 4 equiv) in MeOH (3 mL) was added **8** (40 mg, 1.0 equiv) and AcOH (0.5 mL). 15 min Later, $NaBH_3CN$ (34.5 mg, 20 eq.) was added in potionwise, and the resulted mixture was stirred at 40 °C for overnight. The reaction mixture was concentrated to remove some MeOH, and then purified by pre-HPLC to give the Boc-protected **C-5**, which is further treated with TFA and concentrated to remove TFA. The final compound **C-5** was obtained as a gray solid 4.7 mg.

[0337] LC-MS: 469.26 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.21 (s, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.72 – 4.55 (m, 2H), 3.51 – 3.39 (m, 4H), 3.24 – 3.13 (m, 2H), 2.99 (s, 3H), 2.96 – 2.83 (m, 1H), 2.83 – 2.74 (m, 1H), 2.60 – 2.46 (m, 1H), 2.22 – 2.03 (m, 3H), 2.03 – 1.94 (m, 2H).

3-(6-oxo-6,8-dihydrospiro[furo[3,4-e]isoindole-3,4'-piperidin]-7(1H)-yl)piperidine-2,6-dione (C7)



Step 1:

[0338] To a solution of 5-Bromo-3H-isobenzofuran-1-one (**C-7.1**) (10 g, 1 eq.) in trifluoromethanesulfonic acid (80 mL, 20 eq.) was added NIS (12.5 g, 1.2 eq.) at 0 °C in portions. The mixture was allowed to warm to room temperature and stirred overnight. TLC showed no starting material remained and two new spots formed. The reaction mixture was poured into ice-water and yellow solid precipitated. The mixture was filtered and the filter cake was washed with ice cold water. The filter cake was dissolved in DCM and dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated to afford a yellow solid. The crude product was purified by silica gel flash chromatography. The less polar product (top spot on TLC) **C-7.2** was obtained as a brown solid (8 g, yield 50%).

Step 2:

[0339] A vial was charged with compound **C-7.2** (8 g, 1 eq.), $Pd(dppf)Cl_2$ (0.2 eq.), K_2CO_3 (3

eq.) and dioxane-H_2O (100 mL/20 mL). The mixture was purged with nitrogen and potassium vinyltrifluoroborate (2.0 eq.) was added into. The reaction was heated to 65 °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 0-50% EtOAc/hexane to give compound **C-7.3** as a yellow foam (3.2 g, yield 57%).

[0340] LC-MS: 239/241 $[M+H]^+$; ^1H NMR (600 MHz, Chloroform-d) δ 7.70 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 6.92 (dd, J = 18.0, 11.6 Hz, 1H), 5.62 (d, J = 11.6 Hz, 1H), 5.42 (d, J = 18.0 Hz, 1H), 5.33 (s, 2H).

Step 3:

[0341] A solution of compound **C-7.3** (5 g) in CH_2Cl_2 (100 mL) was cooled to -78 °C then O_3 was bubbled into this solution. The passage of O_3 was continued for a further 30 min until the color turned pale blue and then air was bubbled into the solution for 10 min to remove excess O_3. After dropwise addition of Me_2S (2 mL), the solution was kept stirred and warmed to room temperature. The mixture was diluted with water and extracted with DCM. The organic layer was washed with brine and dried over $MgSO_4$. The residue was quickly purified by chromatography to give compound **C-7.4** (4 g).

Step 4:

[0342] To a solution of compound **C-7.4** (4 g, 1.0 eq.) in MeOH (40 mL, 10V) was added $NaBH_4$ (1.9 g, 3 eq.) at 0 °C in portions. TLC indicated compound **4** was consumed completely and LCMS indicated there was desired product. The reaction mixture was quenched by addition H_2O at 20 °C, and then concentrated under reduced pressure to remove MeOH. Then the mixture was extracted with EtOAc). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/1 to Ethyl acetate) to give compound **C-7.5** (3 g, yield 75%).

Step 5:

[0343] A round bottomed flask equipped with a stirrer bar was charged with a mixture of compound **C-7.5** (4 g, 1.0 eq.), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (7.7 g, 1.5 eq.), potassium carbonate (6.9 g, 3.0 eq.), and Pd(dppf)Cl_2 (2.4 g, 0.2 eq.). The flask was evacuated and back-filled with nitrogen (x 3). The mixture of dioxane-H_2O (100 mL/20 mL) was added and kept stirred at 90 °C for 10 hours. The cooled reaction mixture was diluted with EtOAc and filtered through Celite™ to remove insoluble material. The filtrate was washed with water, saturated aqueous sodium chloride and

then dried over magnesium sulfate, filtered and the filtrate concentrated. The crude material was purified by flash silica chromatography, elution gradient MeOH in DCM. Pure fractions were combined and concentrated to afford compound **C-7.6** (5 g, 89%).

Step 6:

[0344] To a mixture of compound **C-7.6** (6 g, 1 eq.) in MeCN (60 mL) was added NBS (3.7, 1.2 eq.) in one portion. The mixture was stirred at 20 °C for 16 h. The mixture was concentrated in vacuum and the crude material was purified by flash silica chromatography, elution gradient MeOH in DCM to give compound **C-7.7** was obtained as a white solid (6.6 g, 90% yield).

[0345] ^{1}H NMR (600 MHz, Chloroform-d) δ 7.87 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 5.25 (s, 2H), 5.16 (d, *J* = 13.0 Hz, 1H), 5.05 (d, *J* = 13.0 Hz, 1H), 4.25 (m, 2H), 4.08 – 3.81 (m, 2H), 3.33 (m, 1H), 2.68 – 2.56 (m, 1H), 1.65 (d, *J* = 13.9 Hz, 1H), 1.50 (s, 9H).

Step 7:

[0346] To a solution of compound **C-7.7** (500 mg, 1.0 eq.) in toluene (10 mL) and MeOH (1 mL) was added n-Bu_3SnH (5.0 eq.) and AIBN (0.1 eq.). The mixture was heated to reflux and stirred overnight. After cooling down, an additional n-Bu_3SnH (5.0 eq.) was added into above mixture and kept stirred at 100 °C for another 12 h. TLC showed no starting material remained and the reaction mixture was poured into saturated aq. KF solution (100 mL) and stirred for 1 h. Then, the reaction mixture was filtered and extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate. The crude product was purified by silica gel column chromatography (PE:EA= 4:1) to give compound **C-7.8** was obtained as a white solid (60% yield). LC-MS: 346 $[M+H]^+$; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 5.39 (s, 2H), 5.09 (s, 2H), 3.98 (brs, 2H), 3.07 (brs, 2H), 1.88 (td, J = 13.1, 4.9 Hz, 2H), 1.64 (dd, J = 13.8, 2.4 Hz, 2H), 1.43 (s, 9H).

Step 8:

[0347] To a solution of compound **C-7.8** (1.25 g, 1 eq.) in tetrahydrofuran (10 mL) and water (10 mL) was added sodium hydroxide (720 mg, 5 eq.). The mixture was stirred at 20 °C for 16 h. TLC (ethyl acetate: hexane = 1:1) showed reaction was complete. The mixture was adjusted to pH = 5-6 with aq. hydrochloric acid (1 M) and extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The crude material **9** was not further purified and used as crude for the next step.

Step 9:

[0348] To a solution of compound **C-7.9** (1 g, crude, 1 eq.) in dichloromethane (50 mL) was added manganese dioxide (20 eq.). The mixture was stirred at 20 °C for about 1 h. TLC showed reaction was complete. The mixture was diluted with dichloromethane and MeOH, then filtered

through a pad of Celite. The filtrate was concentrated in vacuum and the crude product **C-7.10** (0.6 g, crude) was used directly in the next step.

Step 10:

[0349] To a mixture of compound **C-7.10** (300 mg, crude, 1.0 eq.) in methanol (5 mL) and dichloromethane (5 mL) was added 3-aminopiperidine-2,6-dione (162 mg, 1.5 eq., HCl salt), AcONa (204 mg, 3.0 eq.) and AcOH (150 μL, 3.0 eq.). The mixture was stirred at 20 °C for 1 h, then sodium cyanoborohydride (104 mg, 2.0 eq.) was added and the mixture was further stirred for 30 min. LCMS showed the reaction was complete. Next, the reaction mixture was concentrated under reduced pressure to give a residue which was purified by pre-HPLC (20% ~ 50% ACN, neutral). The desired product **C-7.11** was obtained as a white solid 120 mg after lyophilization.

Step 11:

[0350] To a solution of compound **C-7.11** (180 mg 1.0 equiv) in DMF (3 mL) was added HATU (216 mg, 1.5 equiv) and DIPEA (0.2 mL, 3.0 equiv) at 0 °C, and the reaction was stirred at rt for 30 min. UPLC-MS indicated a new main peak with desired MS formed, then quenched with water and the mixture was extracted with ethyl acetate, washed with brine, and then dried over sodium sulfate. The target compound **C-7.12** was obtained as a brown solid (100 mg, 60% yield).

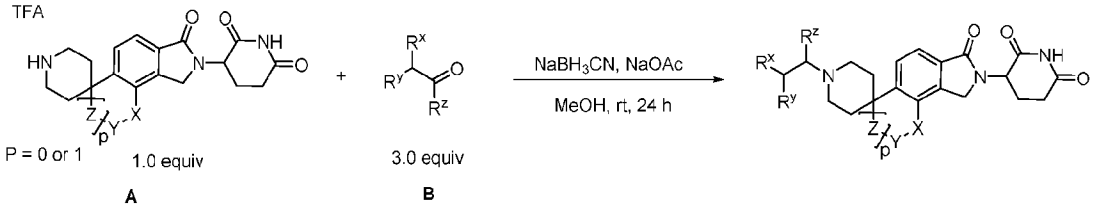
[0351] LC-MS: 456 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 11.01 (s, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 5.16 – 5.11 (m, 1H), 5.08 (m, 2H), 4.44 (d, J = 17.4 Hz, 1H), 4.29 (d, J = 17.4 Hz, 1H), 3.98 (m, 2H), 3.04 (m, 3H), 2.60 (d, J = 17.0 Hz, 1H), 2.42 – 2.31 (m, 1H), 2.04 – 1.93 (m, 1H), 1.92 – 1.80 (m, 2H), 1.64 (m, 2H), 1.43 (s, 9H).

Step 12:

[0352] Compound **C-7.12** was treated with TFA in DCM at room temperature to de-protect the N-Boc group to provide the cereblon ligand **C-7**.

LC/MS (ESI) m/z: 355.1.

Synthetic procedures for preparing IKZF2 degraders 3-362



[0353] To a solution of **A** (0.02 mmol) in MeOH (4 mL) was added NaOAc (0.06 mmol), followed by **B** (0.06 mmol). After being stirred at rt for 30 min, 5 equivalent $NaBH_3CN$ (0.10 mmol) was added. 12 h later, additional 5 equivalent $NaBH_3CN$ (0.1 mmol) was added. The result reaction mixture was kept stirred for additional 12 h. Then the solvent was removed under reduced pressure, and the result residue was purified by pre-HPLC to obtain the title compounds **3-362**.

II. Characterization of Compounds

[0354] Characterizational Data of the compounds is shown in Table E2.

Table E1. Characterization Data

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
A1	356.15	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.28 (s, 1H), 5.23 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.55 (d, *J* = 1.4 Hz, 2H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.32 (d, *J* = 16.0 Hz, 1H), 4.15 (s, 2H), 3.01 – 2.77 (m, 4H), 2.38 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.29 – 2.17 (m, 1H), 1.92 (t, *J* = 12.5 Hz, 2H), 1.83 – 1.72 (m, 2H).
A2	370.17	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.45 (d, *J* = 1.2 Hz, 2H), 5.22 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.40 (d, *J* = 16.4 Hz, 1H), 4.31 – 4.20 (m, 3H), 4.11 (brs, 1H), 3.06 – 2.78 (m, 4H), 2.37 (qd, *J* = 13.1, 5.0 Hz, 1H), 2.22 (dtd, *J* = 13.1, 5.3, 2.7 Hz, 1H), 2.17 – 2.04 (m, 3H), 1.60-1.50 (s, 4H).
A3	496.16	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.73 (t, *J* = 6.4 Hz, 4H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 55.9 Hz, 1H), 5.15 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.73 (s, 2H), 4.45 (d, *J* = 12.3 Hz, 3H), 3.59 (d, *J* = 12.8 Hz, 2H), 3.41 – 3.36 (m, 1H), 3.22 (d, *J* = 13.1 Hz, 2H), 2.92 (ddd, *J* = 18.5, 13.5, 5.4 Hz, 1H), 2.80 (ddd, *J* = 17.6, 4.7, 2.4 Hz, 1H), 2.52 (qd, *J* = 13.3, 4.8 Hz, 1H), 2.34 – 2.01 (m, 5H).
A4	498.15	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.64 (t, *J* = 8.1 Hz, 1H), 7.52 – 7.25 (m, 4H), 5.15 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.71 (s, 2H), 4.47 (dd, *J* = 17.3, 12.2 Hz, 3H), 3.62 (d, *J* = 12.8 Hz, 2H), 3.31 – 3.09 (m, 2H), 2.92 (ddd, *J* = 18.4, 13.4, 5.4 Hz, 1H), 2.80 (ddd, *J* = 17.6, 4.7, 2.4 Hz, 1H), 2.52 (qd, *J* = 13.2, 4.7 Hz, 1H), 2.38 – 2.01 (m, 5H).
A5	482.21	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.62 – 7.28 (m, 5H), 5.15 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.72 (s, 2H), 4.50 – 4.32 (m, 3H), 3.59 (d, *J* = 12.8 Hz, 2H), 3.41 – 3.36 (m, 1H), 3.31 – 3.09 (m, 2H), 2.92

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
		(ddd, *J* = 17.6, 13.5, 5.4 Hz, 1H), 2.80 (ddd, *J* = 17.5, 4.7, 2.4 Hz, 1H), 2.52 (qd, *J* = 13.2, 4.7 Hz, 1H), 2.34 – 2.04 (m, 5H).
A6	510.21	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.76 (dd, *J* = 8.7, 5.9 Hz, 1H), 7.50 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.31 (td, *J* = 8.3, 2.6 Hz, 2H), 5.16 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.74 (s, 2H), 4.57 (s, 2H), 4.53 – 4.38 (m, 2H), 3.65 (d, *J* = 12.8 Hz, 2H), 3.41 – 3.36 (m, 2H), 2.92 (ddd, *J* = 17.6, 13.4, 5.4 Hz, 1H), 2.80 (ddd, *J* = 17.6, 4.7, 2.5 Hz, 1H), 2.52 (qd, *J* = 13.2, 4.7 Hz, 1H), 2.30 (t, *J* = 14.1 Hz, 2H), 2.23 – 2.04 (m, 3H).
A7	452.25	
A8	446.20	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.55 (t, *J* = 2.4 Hz, 5H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.0 Hz, 1H), 5.15 (dd, *J* = 13.4, 5.2 Hz, 1H), 4.73 (s, 2H), 4.45 (d, *J* = 12.3 Hz, 2H), 4.40 (s, 2H), 3.59 (d, *J* = 12.9 Hz, 2H), 3.21 (t, *J* = 13.0 Hz, 2H), 2.92 (ddd, *J* = 17.6, 13.5, 5.4 Hz, 1H), 2.80 (ddd, *J* = 17.6, 4.7, 2.4 Hz, 1H), 2.52 (qd, *J* = 13.2, 4.7 Hz, 1H), 2.31 – 2.14 (m, 3H), 2.10 (d, *J* = 15.0 Hz, 2H).
A9	510.21	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.72 (s, 4H), 7.56 – 7.46 (m, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 6.86 (t, *J* = 55.9 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.62 – 4.25 (m, 6H), 3.48 (d, *J* = 12.8 Hz, 2H), 3.42 – 3.34 (m, 2H), 2.91 (ddd, *J* = 17.6, 13.4, 5.3 Hz, 1H), 2.79 (ddd, *J* = 17.6, 4.7, 2.4 Hz, 1H), 2.60 – 2.32 (m, 3H), 2.30 – 2.10 (m, 3H), 2.05 – 1.79 (m, 2H).
A10	512.17	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 – 7.32 (m, 5H), 5.14 (dt, *J* = 13.3, 5.0 Hz, 1H), 4.54 – 4.43 (m, 2H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.35 – 4.27 (m, 2H), 3.54 (d, *J* = 12.2 Hz, 2H), 3.48 – 3.35 (m, 3H), 2.92 (ddd, *J* = 18.5, 13.4, 5.3 Hz, 1H), 2.79 (ddd, *J* = 17.5, 4.7, 2.4 Hz, 1H), 2.60 – 2.33 (m, 3H), 2.33 – 2.11 (m, 3H), 2.00 (d, *J* = 15.0 Hz, 2H).
A11	488.25	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.60 – 7.25 (m, 6H), 5.13 (dd, *J* = 13.3, 5.0 Hz, 1H), 4.64 – 4.15 (m, 6H), 3.47 (d, *J* = 13.0 Hz, 2H), 3.43 – 3.34 (m, 2H), 2.91 (ddd, *J* = 18.4, 13.4, 5.3 Hz, 1H), 2.85 – 2.63 (m, 3H), 2.62 – 2.46 (m, 1H), 2.39 (t, *J* = 13.3 Hz, 2H), 2.30 – 2.11 (m, 3H), 1.97 (d, *J* = 14.9 Hz, 2H), 1.37 – 1.14 (m, 3H).
A12	474.23	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.56 – 7.26 (m, 6H), 5.13 (dd, *J* = 13.3, 5.0 Hz, 1H), 4.52 – 4.25 (m, 6H), 3.45 (m, 2H), 3.35-3.30 (m, 2H), 2.91 (ddd, *J* = 18.5, 13.4, 5.3 Hz, 1H), 2.79 (ddd, *J* = 17.7, 4.8, 2.4 Hz, 1H), 2.53 (td, *J* = 13.2, 4.7 Hz,

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
		1H), 2.40 (m, 5H), 2.29 – 2.10 (m, 3H), 1.97 (d, *J* = 14.7 Hz, 2H).
A13	460.22	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.68 – 7.45 (m, 6H), 7.36 (d, *J* = 8.0 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.52 – 4.23 (m, 5H), 3.56 – 3.42 (m, 2H), 3.33 (dq, *J* = 3.3, 1.8 Hz, 3H), 2.91 (ddd, *J* = 17.5, 13.4, 5.3 Hz, 1H), 2.79 (ddd, *J* = 17.7, 4.7,A 2.5 Hz, 1H), 2.60 – 2.47 (m, 1H), 2.47 – 2.31 (m, 2H), 2.30 – 2.11 (m, 3H), 2.04 – 1.87 (m, 2H).
A14	466.26	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.54 (dd, *J* = 7.9, 5.4 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 5.14 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.50 – 4.28 (m, 3H), 3.58 (d, *J* = 13.2 Hz, 2H), 3.29 – 3.19 (m, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.92 (ddd, *J* = 18.6, 13.5, 5.4 Hz, 1H), 2.80 (ddd, *J* = 17.5, 4.7, 2.4 Hz, 1H), 2.60 – 2.38 (m, 3H), 2.29 – 2.11 (m, 3H), 1.88 (ddt, *J* = 45.6, 31.1, 14.9 Hz, 8H), 1.49 – 1.20 (m, 4H), 1.20 – 0.99 (m, 2H).
A15	460.22	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.44 (dd, *J* = 7.8, 3.4 Hz, 3H), 7.35 (dd, *J* = 11.3, 7.8 Hz, 3H), 5.15 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.72 (s, 2H), 4.54 – 4.38 (m, 2H), 4.35 (s, 2H), 3.58 (d, *J* = 13.2 Hz, 2H), 3.27 – 3.11 (m, 2H), 2.92 (ddd, *J* = 18.5, 13.4, 5.4 Hz, 1H), 2.80 (ddd, *J* = 17.6, 4.7, 2.4 Hz, 1H), 2.57 (d, *J* = 4.7 Hz, 1H), 2.42 (s, 3H), 2.07 (d, *J* = 9.1 Hz, 5H).
A16	474.23	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.55 – 7.27 (m, 6H), 5.15 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.76 (s, 2H), 4.45 (d, *J* = 12.6 Hz, 2H), 4.36 (s, 2H), 3.58 (d, *J* = 12.9 Hz, 2H), 3.26 – 3.11 (m, 2H), 2.92 (ddd, *J* = 18.5, 13.5, 5.4 Hz, 1H), 2.82 (dd, *J* = 4.8, 2.5 Hz, 1H), 2.80 – 2.65 (m, 2H), 2.52 (qd, *J* = 13.3, 4.9 Hz, 1H), 2.30 – 2.01 (m, 5H), 1.27 (t, *J* = 7.6 Hz, 3H).
A17	488.23	
A18	438.25	
A19	480.28	
A20	454.25	
A21	500.17	
A22	486.21	
A23	504.22	
A24	464.26	
A25	522.10	

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
A26	478.21	
A27	496.18	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.30 (d, J = 8.5 Hz, 1H), 8.09 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 7.0 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.68 – 7.59 (m, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 7.7 Hz, 1H), 5.13 (dd, J = 13.4, 5.1 Hz, 1H), 4.90 (s, 2H), 4.75 (s, 2H), 4.51 – 4.35 (m, 2H), 3.69 – 3.59 (m, 2H), 3.44 – 3.33 (m, 2H), 2.96 – 2.84 (m, 1H), 2.82 – 2.72 (m, 1H), 2.57 – 2.42 (m, 1H), 2.30 – 2.12 (m, 3H), 2.11 – 2.02 (m, 2H).
A28	482.16	
A29	464.22	
A30	510.15	
A31	474.23	
A32	480.17	
A33	505.11	
A34	496.14	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.08 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 8.00 – 7.92 (m, 2H), 7.68 – 7.58 (m, 3H), 7.40 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.72 (s, 2H), 4.56 (s, 2H), 4.50 – 4.36 (m, 2H), 3.68 – 3.57 (m, 2H), 3.29 – 3.18 (m, 2H), 2.98 – 2.83 (m, 1H), 2.82 – 2.72 (m, 1H), 2.49 (qd, J = 13.2, 4.7 Hz, 1H), 2.33 – 2.12 (m, 3H), 2.12 – 2.02 (m, 2H).
A35	514.10	
A36	514.11	
A37	530.07	
A38	497.14	
A39	497.15	
A40	497.15	
A41	497.17	^{1}H NMR (400 MHz, Methanol-d_4) δ 9.12 – 9.02 (m, 1H), 8.48 (dd, J = 8.4, 1.7 Hz, 1H), 8.14 (dd, J = 8.3, 1.3 Hz, 1H), 8.03 – 7.90 (m, 1H), 7.76 – 7.66 (m, 2H), 7.49 – 7.28 (m, 2H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.99 (s, 2H), 4.74 (s, 2H), 4.51 – 4.36 (m, 2H), 3.73 – 3.60 (m, 2H), 3.44 – 3.33 (m, 2H), 2.96 – 2.84 (m, 1H), 2.83 – 2.72 (m, 1H), 2.57 – 2.43 (m, 1H), 2.38 – 2.24 (m, 2H), 2.21 – 2.12 (m, 1H), 2.12 – 2.02 (m, 2H).

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
A42	497.14	
A43	497.09	
A44	497.08	
A45	497.16	
A46	497.16	
A47	498.16	
A48	498.16	
A49	486.18	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.40 (s, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.43 – 7.36 (m, 2H), 7.29 (d, J = 7.7 Hz, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.79 – 4.67 (m, 4H), 4.52 – 4.34 (m, 2H), 3.71 – 3.58 (m, 2H), 3.39 – 3.32 (m, 2H), 2.97 – 2.83 (m, 1H), 2.83 – 2.73 (m, 1H), 2.58 – 2.43 (m, 1H), 2.30 – 2.13 (m, 3H), 2.13 – 2.04 (m, 2H).
A50	514.09	
A51	500.08	
A52	486.14	
A53	500.09	
A54	502.98	
A56	486.09	
A57	500.05	^{1}H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.13 (s, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.81 (s,1 H), 7.46 - 7.17 (m, 3H), 5.19 – 5.03 (m, 1H), 4.68 (s, 2H), 4.52 (s, 2H), 4.40 (d, J = 17.0 Hz, 1H), 4.24 (d, J = 17.3 Hz, 1H), 4.09 (s, 3H), 3.44 (brs, 2H), 3.21 (brs, 2H), 2.92 (t, J = 12.7 Hz, 1H), 2.60 (d, J = 17.7 Hz, 1H), 2.43 (d, J = 12.5 Hz, 1H), 2.28 – 1.85 (m, 5H)
A58	486.10	
A59	485.10	
A60	487.06	
A62	503.02	
A64	497.10	
A65	497.08	
A66	486.09	

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
A67	500.10	
A68	500.11	
A69	500.08	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.42 (s, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.78 (s, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.14 (dd, J = 8.6, 1.3 Hz, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.67 (s, 2H), 4.50 – 4.35 (m, 3H), 4.29 – 4.16 (m, 4H), 3.23 – 3.10 (m, 2H), 2.99 – 2.84 (m, 1H), 2.64 – 2.54 (m, 1H), 2.47 – 2.38 (m, 1H), 2.20 – 2.05 (m, 2H), 2.03 – 1.91 (m, 3H).
A70	486.15	
A71	486.14	
A72	500.10	
A73	486.12	
A74	499.12	
A75	500.12	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.34 (s, 1H), 7.87 (dd, J = 8.4, 0.8 Hz, 1H), 7.49 (d, J = 6.8 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.19 (dd, J = 8.4, 6.9 Hz, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.72 (s, 3H), 4.51 – 4.35 (m, 2H), 4.30 (s, 3H), 3.73 – 3.63 (m, 2H), 3.37 – 3.33 (m, 1H), 3.30 – 3.26 (m, 1H), 2.96 – 2.84 (m, 1H), 2.83 – 2.73 (m, 1H), 2.57 – 2.43 (m, 1H), 2.32 – 2.12 (m, 3H), 2.12 – 2.02 (m, 2H).
A76	486.13	
A77	486.09	
A78	486.11	
A79	486.29	
A80	486.14	
A81	529.23	
A82	529.06	
A83	513.13	
A84	512.12	
A85	529.09	
A86	538.11	
A87	485.11	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.60 – 7.53 (m, 1H), 7.43 (d, J = 3.2 Hz, 1H), 7.39 (d, J = 7.7

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
		Hz, 1H), 7.32 – 7.23 (m, 3H), 6.79 – 6.74 (m, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.75 – 4.67 (m, 2H), 4.64 (s, 2H), 4.53 – 4.35 (m, 2H), 3.69 – 3.57 (m, 2H), 3.30 – 3.23 (m, 2H), 2.96 – 2.83 (m, 1H), 2.82 – 2.73 (m, 1H), 2.56 – 2.42 (m, 1H), 2.28 – 2.11 (m, 3H), 2.10 – 2.00 (m, 2H).
A88	502.16	
A89	528.14	
A90	512.08	
A91	525.92	
A92	490.10	
A93	478.21	
A94	496.19	
A95	503.08	
A96	515.15	
A97	531.09	
A98	476.09	
A99	490.07	
A100	538.07	
A101	539.07	
A102	522.10	
A103	523.09	
A104	512.08	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.04 (s, 2H), 7.85 – 7.73 (m, 2H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.48 – 7.36 (m, 2H), 7.31 (d, *J* = 7.7 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.77 – 4.67 (m, 2H), 4.53 – 4.32 (m, 4H), 3.68 – 3.50 (m, 2H), 3.28 – 3.15 (m, 2H), 2.97 – 2.83 (m, 1H), 2.83 – 2.72 (m, 1H), 2.57 – 2.42 (m, 1H), 2.32 – 2.00 (m, 5H).
A105	526.12	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.02 (s, 1H), 7.88 (d, *J* = 0.7 Hz, 1H), 7.77 – 7.67 (m, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.31 (d, *J* = 7.7 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.75 – 4.66 (m, 2H), 4.51 – 4.33 (m, 4H), 3.61 (d, *J* = 13.0 Hz, 2H), 3.28 – 3.15 (m, 2H), 2.97 – 2.83 (m, 1H), 2.82 – 2.72 (m, 1H), 2.56 – 2.43 (m, 1H), 2.35 – 2.02 (m, 5H).
A106	529.04	

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
A107	512.09	
A108	512.07	
A109	498.07	
A110	503.05	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.48 (d, J = 3.2 Hz, 1H), 7.46 – 7.37 (m, 2H), 7.35 – 7.25 (m, 1H), 7.21 – 7.09 (m, 1H), 6.60 (d, J = 3.2 Hz, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.73 (s, 2H), 4.63 (s, 2H), 4.50 – 4.35 (m, 2H), 3.71 – 3.60 (m, 2H), 3.30 – 3.19 (m, 2H), 2.96 – 2.84 (m, 1H), 2.83 – 2.73 (m, 1H), 2.57 – 2.42 (m, 1H), 2.28 – 2.05 (m, 5H).
A111	513.09	
A112	490.20	
A113	488.17	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.50 – 7.39 (m, 4H), 7.36 – 7.28 (m, 1H), 5.31 – 5.06 (m, 5H), 4.72 (s, 2H), 4.55 – 4.37 (m, 2H), 4.34 (s, 2H), 3.67 – 3.55 (m, 2H), 3.26 – 3.18 (m, 2H), 2.93 – 2.86 (m, 1H), 2.82 – 2.74 (m, 1H), 2.57 – 2.43 (m, 1H), 2.32 – 2.04 (m, 5H).
A114	553.16	
A115	486.18	
A116	486.22	
A117	504.06	
A118	504.07	
A119	486.11	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (d, J = 2.3 Hz, 1H), 7.74 – 7.66 (m, 1H), 7.54 – 7.46 (m, 2H), 7.41 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.24 – 7.18 (m, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.73 (s, 2H), 4.65 (s, 2H), 4.51 – 4.35 (m, 2H), 3.69 – 3.55 (m, 2H), 3.30 – 3.27 (m, 2H), 2.99 – 2.84 (m, 1H), 2.83 – 2.72 (m, 1H), 2.58 – 2.43 (m, 1H), 2.29 – 2.04 (m, 5H).
A120	486.09	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (d, J = 2.2 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 6.95 (dd, J = 2.2, 1.0 Hz, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.71 (s, 2H), 4.53 – 4.36 (m, 4H), 3.65 – 3.49 (m, 2H), 3.26 – 3.15 (m, 2H), 2.96 – 2.84 (m, 1H), 2.82 – 2.73 (m, 1H), 2.58 – 2.43 (m, 1H), 2.28 – 2.13 (m, 3H), 2.13 – 2.03 (m, 2H).

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
A121	499.13	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.46 – 7.37 (m, 2H), 7.28 (d, J = 7.7 Hz, 1H), 7.21 – 7.12 (m, 2H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.75 – 4.67 (m, 2H), 4.57 (s, 2H), 4.53 – 4.36 (m, 3H), 3.66 – 3.57 (m, 2H), 3.30 – 3.21 (m, 2H), 2.96 – 2.84 (m, 1H), 2.82 – 2.73 (m, 1H), 2.56 – 2.43 (m, 4H), 2.28 – 2.12 (m, 3H), 2.11 – 2.01 (m, 2H).
A122	501.04	
A123	529.11	
A124	513.10	
A125	513.10	
A126	526.11	
A127	563.92	
A128	520.02	
A129	485.10	
A130	499.12	
A131	501.02	
A132	523.12	
A133	523.11	
A134	526.08	
A135	553.16	
A136	504.03	
A137	503.07	
A138	515.11	
A139	526.06	
A140	518.02	
A141	519.04	
A142	520.02	
A143	500.12	
A144	526.10	
A145	540.09	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.10 – 8.06 (m, 1H), 7.89 (d, J = 0.7 Hz, 1H), 7.76 (s, 1H), 7.73 – 7.68 (m, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.31 (d, J = 7.7 Hz, 1H), 5.13 (dd, J = 13.3, 5.2 Hz, 1H), 4.71 (s, 2H), 4.51 – 4.34 (m,

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
		4H), 4.23 (q, *J* = 7.3 Hz, 2H), 3.67 – 3.55 (m, 2H), 3.27 – 3.15 (m, 2H), 2.95 – 2.82 (m, 1H), 2.82 – 2.73 (m, 1H), 2.35 – 2.20 (m, 2H), 2.20 – 2.11 (m, 1H), 2.11 – 2.01 (m, 2H), 1.50 (t, *J* = 7.3 Hz, 3H).
A146	554.13	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.11 (d, *J* = 0.8 Hz, 1H), 7.90 (d, *J* = 0.8 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.31 (d, *J* = 7.7 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.72 (s, 2H), 4.62 – 4.54 (m, 1H), 4.51 – 4.36 (m, 4H), 3.67 – 3.56 (m, 2H), 3.27 – 3.16 (m, 2H), 2.97 – 2.84 (m, 1H), 2.83 – 2.72 (m, 1H), 2.57 – 2.43 (m, 1H), 2.30 – 2.05 (m, 5H), 1.54 (d, *J* = 6.7 Hz, 6H).
A147	596.10	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.18 – 8.12 (m, 1H), 7.92 (d, *J* = 0.6 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.47 – 7.36 (m, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.72 (s, 2H), 4.51 – 4.34 (m, 5H), 4.14 – 4.03 (m, 2H), 3.68 – 3.54 (m, 4H), 3.28 – 3.15 (m, 2H), 2.98 – 2.83 (m, 1H), 2.82 – 2.72 (m, 1H), 2.57 – 2.43 (m, 1H), 2.30 – 2.02 (m, 9H).
A148	526.11	
A149	512.09	
A150	514.08	
A151	528.09	
A152	501.10	
A153	517.10	
A154	576.07	
A155	526.11	
A156	512.12	
A157	553.07	
A158	529.04	
A159	539.05	
A160	512.10	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.98 (s, 1H), 7.96 – 7.91 (m, 1H), 7.74 (d, *J* = 2.3 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 2.3 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.71 (s, 2H), 4.51 – 4.35 (m, 4H), 3.68 – 3.51 (m, 2H), 3.29 – 3.16 (m, 2H), 2.96 – 2.83 (m, 1H), 2.82

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
		– 2.72 (m, 1H), 2.58 – 2.43 (m, 1H), 2.32 – 2.12 (m, 3H), 2.12 – 2.03 (m, 2H).
A161	568.09	
A162	512.11	
A163	486.05	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.36 (s, 1H), 8.22 (s, 1H), 7.53 (d, J = 3.5 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 6.61 (d, J = 3.5 Hz, 1H), 5.13 (dd, J = 13.3, 5.2 Hz, 1H), 4.71 (s, 2H), 4.59 – 4.34 (m, 4H), 3.70 – 3.50 (m, 2H), 3.29 – 3.16 (m, 2H), 2.97 – 2.84 (m, 1H), 2.83 – 2.72 (m, 1H), 2.57 – 2.42 (m, 1H), 2.29 – 2.04 (m, 5H).
A164	528.06	
A165	503.04	
A166	597.05	
A167	556.07	
A168	553.07	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 – 8.09 (m, 1H), 7.76 – 7.69 (m, 1H), 7.66 (s, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.41 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.04 – 6.94 (m, 1H), 6.89 (d, J = 8.4 Hz, 1H), 5.44 (s, 2H), 5.13 (dd, J = 13.3, 5.2 Hz, 1H), 4.70 (s, 2H), 4.55 – 4.34 (m, 4H), 3.63 – 3.50 (m, 2H), 3.19 (t, J = 13.2 Hz, 2H), 2.97 – 2.84 (m, 1H), 2.83 – 2.72 (m, 1H), 2.58 – 2.42 (m, 1H), 2.30 – 2.13 (m, 3H), 2.12 – 2.02 (m, 2H).
A169	500.08	
A170	526.17	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.13 (s, 1H), 7.84 (d, J = 0.7 Hz, 1H), 7.49 (s, 1H), 7.47 – 7.38 (m, 2H), 7.35 – 7.23 (m, 2H), 7.16 (d, J = 7.6 Hz, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.53 (s, 2H), 4.37 (d, J = 17.1 Hz, 1H), 4.21 (d, J = 17.1 Hz, 1H), 3.87 (s, 3H), 3.51 (s, 2H), 2.98 – 2.76 (m, 3H), 2.63 – 2.54 (m, 1H), 2.48 – 2.35 (m, 1H), 2.13 – 2.00 (m, 2H), 2.00 – 1.86 (m, 3H), 1.76 – 1.60 (m, 2H).
A171	501.12	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.71 (s, 2H), 4.58 – 4.35 (m, 6H), 3.64 – 3.50 (m, 2H), 3.29 – 3.16 (m, 2H), 2.97 – 2.84 (m, 1H), 2.83 – 2.73 (m, 1H), 2.57 – 2.43 (m, 1H), 2.30 – 2.12 (m, 3H), 2.12 – 2.02 (m, 2H).

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
A172	485.14	
A173	500.94	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.45 – 7.36 (m, 2H), 7.31 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 7.07 (s, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.70 (s, 2H), 4.51 – 4.33 (m, 4H), 3.66 – 3.53 (m, 4H), 3.23 – 3.12 (m, 2H), 2.98 – 2.84 (m, 1H), 2.83 – 2.73 (m, 1H), 2.57 – 2.43 (m, 1H), 2.32 – 2.03 (m, 5H).
A174	552.10	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.12 (t, J = 0.6 Hz, 1H), 7.88 (d, J = 0.9 Hz, 1H), 7.76 – 7.69 (m, 2H), 7.51 (t, J = 7.7 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.31 (d, J = 7.6 Hz, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.75 – 4.68 (m, 2H), 4.52 – 4.33 (m, 4H), 3.71 (tt, J = 7.3, 3.9 Hz, 1H), 3.65 – 3.56 (m, 2H), 3.26 – 3.16 (m, 2H), 2.97 – 2.84 (m, 1H), 2.84 – 2.72 (m, 1H), 2.58 – 2.42 (m, 1H), 2.31 – 2.05 (m, 5H).
A175	517.05	
A176	503.06	
A177	595.11	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.11 (s, 1H), 8.01 – 7.90 (m, 2H), 7.61 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 7.9 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.32 (d, J = 7.7 Hz, 2H), 7.12 – 6.98 (m, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.72 (s, 2H), 4.55 – 4.31 (m, 4H), 3.89 (s, 3H), 3.69 – 3.56 (m, 2H), 3.27 – 3.12 (m, 2H), 2.97 – 2.84 (m, 1H), 2.83 – 2.72 (m, 1H), 2.58 – 2.42 (m, 1H), 2.33 – 2.03 (m, 5H).
A178	598.99	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13 (s, 1H), 7.99 – 7.91 (m, 2H), 7.68 – 7.60 (m, 1H), 7.58 – 7.50 (m, 3H), 7.42 (d, J = 7.7 Hz, 1H), 7.37 – 7.27 (m, 2H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.77 – 4.66 (m, 2H), 4.51 – 4.35 (m, 4H), 3.68 – 3.57 (m, 2H), 3.29 – 3.16 (m, 2H), 2.98 – 2.84 (m, 1H), 2.83 – 2.72 (m, 1H), 2.59 – 2.42 (m, 1H), 2.33 – 2.04 (m, 5H).
A179	579.09	
A180	486.13	
A181	528.13	
A182	452.03	
A183	452.03	
A184	502.05	
A185	502.03	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.08 (d, J = 8.1 Hz, 1H), 8.05 – 7.99 (m, 2H), 7.62 – 7.53 (m, 1H), 7.53 – 7.46 (m, 1H), 7.41 (d, J = 7.7 Hz, 1H),

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
		7.29 (d, *J* = 7.5 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.77 – 4.63 (m, 4H), 4.54 – 4.34 (m, 2H), 3.71 – 3.58 (m, 2H), 3.28 – 3.17 (m, 2H), 2.98 – 2.83 (m, 1H), 2.82 – 2.71 (m, 1H), 2.56 – 2.41 (m, 1H), 2.28 – 2.05 (m, 5H).
A186	502.04	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.11 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 5.6 Hz, 1H), 7.78 (d, *J* = 5.7 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.80 – 4.68 (m, 4H), 4.53 – 4.34 (m, 2H), 3.68 – 3.57 (m, 2H), 3.39 – 3.32 (m, 2H), 2.97 – 2.83 (m, 1H), 2.82 – 2.73 (m, 1H), 2.58 – 2.41 (m, 1H), 2.30 – 2.12 (m, 3H), 2.11 – 2.01 (m, 2H).
A187	502.05	
A188	502.06	
A189	502.04	
A190	531.97	
A191	488.26	
A192	464.20	
A193	526.51	
A194	514.22	
A195	471.19	
A196	485.20	
A197	512.40	
A198	486.24	
A199	504.24	
A200	504.26	
A201	517.24	
A202	491.22	
A203	488.28	
A204	486.24	
A205	486.24	
A206	448.20	
A207	486.24	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.51 – 7.23 (m, 5H), 5.15 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.74 (s,

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
		2H), 4.60 – 4.27 (m, 4H), 3.62 (t, *J* = 10.0 Hz, 2H), 3.26 (t, *J* = 13.0 Hz, 2H), 3.09 (t, *J* = 7.4 Hz, 2H), 3.02 (t, *J* = 7.4 Hz, 2H), 2.92 (ddd, *J* = 17.6, 13.5, 5.4 Hz, 1H), 2.80 (ddd, *J* = 17.6, 4.7, 2.4 Hz, 1H), 2.59 – 2.44 (m, 1H), 2.38 – 2.04 (m, 7H).
A208	500.26	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.43 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 6.0 Hz, 2H), 7.28 – 7.19 (m, 2H), 5.15 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.80 – 4.70 (m, 2H), 4.54 – 4.34 (m, 4H), 3.65 (d, *J* = 12.9 Hz, 2H), 3.28 (d, *J* = 12.8 Hz, 2H), 3.01 – 2.73 (m, 6H), 2.60 – 2.43 (m, 1H), 2.28 (t, *J* = 14.4 Hz, 2H), 2.19 (ddq, *J* = 10.5, 5.3, 2.7 Hz, 1H), 2.09 (d, *J* = 14.9 Hz, 2H), 1.94 (p, *J* = 6.4 Hz, 2H), 1.90 – 1.77 (m, 2H).
A209	526.26	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.95 (s, 1H), 7.72 (s, 1H), 7.46 – 7.26 (m, 7H), 5.40 (s, 2H), 5.15 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.69 (s, 2H), 4.57 – 4.37 (m, 3H), 4.31 (s, 2H), 3.62 (d, *J* = 12.9 Hz, 2H), 3.10 (d, *J* = 13.1 Hz, 2H), 2.97 – 2.86 (m, 1H), 2.80 (ddd, *J* = 17.6, 4.7, 2.4 Hz, 1H), 2.52 (qd, *J* = 13.2, 4.8 Hz, 1H), 2.26 – 2.06 (m, 5H).
A210	553.21	
A211	476.20	
A212	476.20	
A213	460.25	
A214	480.20	
A215	476.20	
A216	480.20	
A217	500.26	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.12 (d, *J* = 0.9 Hz, 1H), 8.03 – 7.95 (m, 1H), 7.76 – 7.70 (m, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 5.15 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.76 – 4.65 (m, 2H), 4.52 – 4.37 (m, 3H), 4.13 (s, 3H), 3.61 (d, *J* = 12.4 Hz, 2H), 3.22 (t, *J* = 13.1 Hz, 2H), 2.92 (ddd, *J* = 18.5, 13.4, 5.4 Hz, 1H), 2.79 (ddd, *J* = 17.8, 4.8, 2.5 Hz, 1H), 2.51 (qd, *J* = 13.2, 4.7 Hz, 1H), 2.30 – 2.13 (m, 2H), 2.08 (d, *J* = 14.9 Hz, 2H).
A218	502.24	
A219	471.20	
A220	518.20	
A221	512.24	

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
A222	512.20	
A223	504.20	
A224	488.26	
A225	490.23	
A226	500.20	
A227	486.24	
A228	450.51	
A229	464.22	
A230	476.22	
A231	490.24	
A232	518.19	
A233	534.24	
A234	524.20	
A235	524.20	
A236	524.20	
A237	544.20	
A238	544.22	
A239	544.20	
A240	560.20	
A241	560.20	
A242	560.20	
A243	546.10	
A244	476.22	
A245	490.20	
A246	512.24	
A247	491.22	
A248	481.16	
A249	481.16	
A250	481.16	
A251	512.21	

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
A252	491.22	
A253	513.22	
A254	513.22	
A255	520.25	
A256	526.24	
A257	484.17	
A258	356.03	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.81 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 5.21 – 5.13 (m, 3H), 4.56 – 4.39 (m, 2H), 3.48 – 3.36 (m, 4H), 2.97 – 2.86 (m, 1H), 2.83 – 2.75 (m, 1H), 2.59 – 2.44 (m, 1H), 2.34 – 2.15 (m, 3H), 2.02 – 1.94 (m, 2H).
A259	526.16	
A260	512.17	
A261	600.83	
A262	595.05	
A263	579.09	
A264	485.14	
A265	568.11	
A266	486.14	
A267	526.14	
A268	552.12	
A269	582.15	
A270	582.26	
A271	582.17	
A272	612.17	
A273	582.16	
A274	582.17	
A275	472.21	
A276	586.16	
A277	598.18	
A278	557.04	

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
A279	582.14	
A280	556.10	
A281	562.08	
A282	580.07	
A283	540.15	
A284	540.16	
A285	542.10	
A286	570.41	
A287	544.28	
A288	536.34	
A289	562.34	
A290	512.11	
A291	529.39	
A292	584.45	
A293	558.36	
A294	556.40	
A295	514.33	
A296	527.36	
A297	596.45	
A298	514.32	
A299	514.31	
A300	503.35	
A301	503.32	
A302	529.36	
A303	515.29	
A304	516.32	
A305	557.34	
A306	369.32	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.21 (s, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.72 – 4.55 (m, 2H), 3.51 – 3.39 (m, 4H), 3.24 – 3.13 (m, 2H), 2.99 (s, 3H), 2.96 – 2.83 (m, 1H), 2.83 – 2.74 (m, 1H),

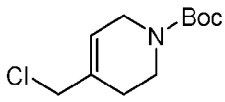
No.	LC-MS: $[M + H]^+$	^{1}H-NMR
		2.60 – 2.46 (m, 1H), 2.22 – 2.03 (m, 3H), 2.03 – 1.94 (m, 2H).
A307	355.27	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.28 – 7.17 (m, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.39 – 4.23 (m, 2H), 3.67 (s, 2H), 3.51 – 3.39 (m, 2H), 3.25 – 3.12 (m, 2H), 2.98 – 2.84 (m, 1H), 2.84 – 2.72 (m, 1H), 2.56 – 2.39 (m, 1H), 2.23 – 1.96 (m, 5H).
A308	539.20	
A309	525.19	
A310	530.16	
A311	530.11	
A312	530.14	
A313	546.20	
A314	546.23	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.51 (s, 1H), 7.93 (s, 1H), 7.89 – 7.75 (m, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 7.7 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.74 (d, J = 11.9 Hz, 2H), 4.53 – 4.33 (m, 4H), 3.69 (d, J = 12.9 Hz, 2H), 3.27 – 3.11 (m, 2H), 3.01 – 2.74 (m, 2H), 2.52 (qd, J = 13.2, 4.8 Hz, 1H), 2.39 – 2.05 (m, 5H).
A315	546.18	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.40 (d, J = 2.5 Hz, 1H), 7.96 – 7.79 (m, 2H), 7.62 – 7.50 (m, 2H), 7.50 – 7.33 (m, 2H), 6.77 (d, J = 2.5 Hz, 1H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.73 (s, 2H), 4.59 – 4.35 (m, 4H), 3.75 (d, J = 12.9 Hz, 2H), 3.27 – 3.20 (m, 2H), 2.98 – 2.73 (m, 2H), 2.61 – 2.43 (m, 1H), 2.40 – 2.05 (m, 5H).
A316	530.24	
A317	446.12	
A318	460.24	
A319	506.09	
A320	520.28	
A321	546.12	
A322	530.22	
A323	530.14	
A324	501.23	
A325	501.18	

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
A326	516.09	
A327	530.20	
A328	586.18	
A329	582.28	
A330	474.20	
A331	546.12	
A332	486.10	
A333	486.13	
A334		
A335	500.24	
A336	576.12	
A337	594.10	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.97 – 7.78 (m, 3H), 7.54 – 7.45 (m, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.29 – 7.13 (m, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.70 (s, 2H), 4.62 – 4.32 (m, 4H), 3.62 (d, J = 12.7 Hz, 2H), 3.24 – 3.06 (m, 2H), 3.00 – 2.75 (m, 2H), 2.57 – 2.46 (m, 1H), 2.36 – 1.99 (m, 5H).
A338	553.12	
A339	553.14	
A340	585.98	
A341	544.12	
A342	544.20	
A343	544.22	
A344	530.24	
A345	530.20	
A346	554.22	
A347	566.14	
A348	566.18	
A349	610.18	
A350	610.11	
A351	534.12	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.46 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.02 (ddt, J = 8.4, 6.7, 2.5 Hz, 2H), 6.84 (ddd, J = 9.0, 6.7, 4.5

No.	LC-MS: $[M + H]^+$	^{1}H-NMR
		Hz, 2H), 4.70-4.60 (m, 2H), 4.55 – 4.37 (m, 3H), 3.63 (d, *J* = 12.9 Hz, 2H), 3.24 – 3.06 (m, 2H), 3.15 (d, *J* = 25.8 Hz, 2H), 3.00 – 2.77 (m, 4H), 2.59 – 2.40 (m, 3H), 2.35 – 1.94 (m, 7H).
A352	610.01	
A353	612.52	
A354	594.18	
A355	594.21	
A356	534.26	
A357	628.10	
A358	534.08	
A359	537.12	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.66 (s, 1H), 8.10 – 8.01 (m, 2H), 7.98 (d, *J* = 1.9 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 5.14 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.68 (s, 2H), 4.53 – 4.31 (m, 4H), 3.67 (t, *J* = 13.1 Hz, 2H), 3.17 (t, *J* = 12.9 Hz, 2H), 2.99 – 2.73 (m, 2H), 2.51 (qd, *J* = 13.2, 4.8 Hz, 1H), 2.40 – 1.88 (m, 5H).
A360	580.18	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.64 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.98 (s, 1H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 5.15 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.73 (s, 2H), 4.57 – 4.34 (m, 4H), 3.70 (d, *J* = 12.9 Hz, 2H), 3.27 – 3.12 (m, 2H), 3.01 – 2.74 (m, 2H), 2.52 (qd, *J* = 13.2, 4.8 Hz, 1H), 2.38 – 2.07 (m, 5H).
A361	522.16	
A362	504.20	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.44 (d, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.19 (dd, *J* = 8.7, 5.3 Hz, 2H), 7.03 (t, *J* = 8.8 Hz, 2H), 5.15 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.71 (s, 2H), 4.58 – 4.34 (m, 2H), 3.75 (d, *J* = 12.8 Hz, 2H), 3.31 – 3.08 (m, 4H), 2.98 – 2.86 (m, 1H), 2.80 (ddd, *J* = 17.6, 4.7, 2.4 Hz, 1H), 2.52 (dd, *J* = 13.1, 4.8 Hz, 1H), 2.30 (d, *J* = 14.6 Hz, 2H), 2.19 (dtd, *J* = 12.9, 5.3, 2.4 Hz, 1H), 2.15 – 2.00 (m, 3H), 1.47 (dt, *J* = 8.0, 5.2 Hz, 1H), 1.20 (ddt, *J* = 29.8, 9.0, 5.4 Hz, 2H).

For Compound B-1 to B-58

Intermediate B1: tert-butyl 4-(chloromethyl)-3,6-dihydro-2H-pyridine-1-carboxylate



Step A: tert-butyl 3-hydroxy-4-methylenepiperidine-1-carboxylate

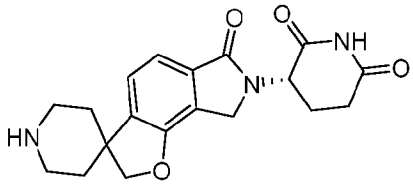
[0355] The suspension of SeO_2 (61.8 g, 558 mmol, 0.55 eq) in DCM (3000 mL) was cooled to -10 °C, before 2-hydroperoxy-2-methyl-propane in H_2O (274 g, 291 mL, 2.10 eq, 70% purity) was added dropwise, and the resulting mixture was stirred for 30 min at -10 °C. The reaction mixture was further cooled to -30 °C, before a solution of compound **5-1** (200 g, 1.01 mol, 1 eq) in DCM (1000 mL) was added dropwise, and the resulting mixture was stirred for another 1 hr at -30 °C. The reaction mixture was warmed to 20 °C, and stirred for further 18 hrs, before the mixture was cooled to 0 °C, and was added ice chips and water (1.0 L). The resulting mixture was stirred at 0 °C for 30 min. The organic phase was separated, and the aqueous phase was extracted with DCM (500 mL), before the combined organic phase was added 10% w/v $NaHSO_3$ solution (1000 mL) portion-wise at 0 °C, during which period the temperature was maintained below 10 °C, and the mixture was stirred for further 5 min after the addition. The organic phase was separated, and the aqueous phase was extracted with DCM (500 mL). The combined organic phase was washed with brine (1000 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate = 100/1 to 1/1). tert-butyl 3-hydroxy-4-methylenepiperidine-1-carboxylate (370 g) was obtained as a white solid and the typical yield was 34.2%. ^1H NMR (400 MHz, DMSO-d_6) δ = 5.22 (br d, J = 3.9 Hz, 1H), 4.98 (s, 1H), 4.79 (s, 1H), 3.93 - 3.76 (m, 2H), 3.71 (td, J = 4.3, 12.6 Hz, 1H), 2.92 - 2.77 (m, 1H), 2.76 - 2.53 (m, 1H), 2.30 (td, J = 3.5, 13.4 Hz, 1H), 2.10 - 1.95 (m, 1H), 1.40 (s, 9H).

Step B: tert-butyl 4-(chloromethyl)-3,6-dihydro-2H-pyridine-1-carboxylate

[0356] To the solution of tert-butyl 3-hydroxy-4-methylenepiperidine-1-carboxylate (100 g, 469 mmol, 1.00 eq) in toluene (2000 mL) was add 2,6-dimethylpyridine (55.2 g, 60.0 mL, 516 mmol, 1.10 eq) at 15 °C. The mixture was cooled to 0 °C, before $SOCl_2$ (66.9 g, 40.8 mL, 563 mmol, 1.20 eq) was added dropwise to the mixture under N_2 atmosphere, during which period the temperature was maintained below 10 °C. The mixture was stirred at 110 °C for 3 hrs, before cooled to 20 °C. Brine (2 x 600 mL) was added and the resulting mixture was stirred at 20 °C for 30 min. The organic phase was separated, before saturated $NaHCO_3$ solution (600 mL) was added portion-wise at 15 °C. The organic phase was separated, washed with brine (1000 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. tert-Butyl 4-(chloromethyl)-3,6-dihydro-2H-pyridine-1-carboxylate (200 g) was obtained as a red oil and

the typical yield was 49.0%. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 5.72 (br s, 1H), 3.98 (s, 2H), 3.88 (br s, 2H), 3.49 (br t, J = 5.6 Hz, 2H), 2.17 (br s, 2H), 1.43 (s, 9H).

Intermediate B2: (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



Step A: Methyl 4-bromo-2-formyl-3-hydroxybenzoate

[0357] The solution of methyl 4-bromo-3-hydroxybenzoate (200 g, 865 mmol, 1.00 eq) in TFA (2.0 L) was added HMTA (485 g, 3.46 mol, 4.00 eq) at 20 °C, before the resulting mixture was stirred at 125 °C for 12 hrs. The mixture was cooled to 20 °C, quenched with 2N HCl solution (5 V), and yellow precipitate was observed. The mixture was stirred for 10 min, before additional H_2O (5 V) was added, and the reaction mixture was stirred for further 1 hr. The mixture was filtered, and the filter cake was dissolved in DCM (2.0 L), filtered over celite, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Methyl 4-bromo-2-formyl-3-hydroxybenzoate (144 g) was obtained as a gray solid, and the typical yield was 64.2%. ^{1}HNMR (400 MHz, DMSO-d_6) δ = 12.06 (br s, 1H), 10.38 (s, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 3.87 (s, 3H).

Step B: (S)-tert-butyl 5-amino-4-(5-bromo-4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate

[0358] To the suspension of methyl 4-bromo-2-formyl-3-hydroxybenzoate (17.3 g, 72.4 mmol, 1.05 eq, HCl salt) in MeOH (300 mL) was added DIPEA (9.37 g, 72.4 mmol, 12.6 mL, 1.05 eq), compound **2**, (17.8 g, 69.0 mmol, 1.00 eq) and AcOH (6.22 g, 103 mmol, 5.92 mL, 1.50 eq) at 20 °C and stirred for 1.5 hrs, before $NaBH_3CN$ (8.67 g, 138 mmol, 2.00 eq) was added portion-wise at 20 °C, and the resulting mixture was stirred at 20 °C for 3 hrs. The mixture was quenched by H_2O (200 mL) at 20 °C and concentrated under reduced pressure. The solvent residue was then extracted with EtOAc (3 x 150 mL), and the combined organic layer was washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate = 1/1 to 100% Ethyl acetate). (S)-tert-butyl 5-amino-4-(5-bromo-4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate (23.0 g) was obtained as a yellow solid and the typical yield was 78.4%. ^{1}H NMR (400 MHz, DMSO-d6) δ = 10.44 (s, 1H), 7.67 - 7.55 (m,

2H), 7.20 (s, 1H), 7.11 (d, J = 7.9 Hz, 1H), 4.76 - 4.67 (m, 1H), 4.58 (d, J = 17.9 Hz, 1H), 4.39 (d, J = 17.9 Hz, 1H), 2.23 - 2.07 (m, 3H), 2.03 - 1.91 (m, 1H), 1.32 (s, 9H).

Step C: (S)-tert-butyl 4-(((2-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-1-oxoisoindolin-4-yl)oxy)methyl)-5,6-dihydropyridine-1(2H)-carboxylate

[0359] To the solution of tert-butyl 4-(chloromethyl)-3,6-dihydro-2H-pyridine-1-carboxylate (150 g, 363 mmol, 1.00 eq) in MeCN (2000 mL) was added K_2CO_3 (150.49 g, 1.09 mmol, 3.00 eq), NaI (5.44 g, 0.36 mmol, 0.10 eq) and (S)-tert-butyl 5-amino-4-(5-bromo-4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate (136 g, 472 mmol, 1.30 eq, 80% purity) at 20 °C. The reaction mixture was stirred at 60 °C for 12 hrs, before being cooled to 20 °C again. The resulting mixture was filtered, and filter cake was washed with DCM (2 x 500 mL). The filtrate was concentrated *in vacuo*, and the crude product was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate = 100/1 to 1/1). (S)-tert-butyl 4-(((2-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-1-oxoisoindolin-4-yl)oxy)methyl)-5,6-dihydropyridine-1(2H)-carboxylate (337 g) was obtained as a red solid, and the typical yield was 72.4%. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 7.67 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 6.33 (br s, 1H), 5.86 (br s, 1H), 5.48 (br s, 1H), 4.90 (dd, J = 6.3, 8.6 Hz, 1H), 4.66 - 4.59 (m, 1H), 4.53 (s, 1H), 4.50 (br s, 2H), 3.98 (br s, 2H), 3.60 (br t, J = 5.5 Hz, 2H), 2.43 - 2.10 (m, 7H), 1.49 (s, 9H), 1.41 (s, 9H).

Step D: tert-butyl 7-[(1S)-4-tert-butoxy-1-carbamoyl-4-oxo-butyl]-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

[0360] To the solution of (S)-tert-butyl 4-(((2-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-1-oxoisoindolin-4-yl)oxy)methyl)-5,6-dihydropyridine-1(2H)-carboxylate (125 g, 205 mmol, 1.00 eq) in toluene (1500 mL) was added AIBN (5.06 g, 0.03 mmol, 0.15 eq) and Bu_3SnH (270 mL, 1.02 mmol, 4.98 eq) at 20 °C. The reaction mixture was stirred at 110 °C for 12 hrs, before being cooled to 20 °C. Saturated KF solution (1000 mL) was added and the resulting mixture was stirred at 20 °C for further 2 hrs. The mixture was filtered and the filter cake was washed by EtOAc (2 x 500 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 x 500 mL). The combined organic phase was washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate = 100/1 to 1/1). tert-Butyl 7-[(1S)-4-tert-butoxy-1-carbamoyl-4-oxo-butyl]-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (160 g) was obtained as a white solid, and the typical yield was 56.6%. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 7.40 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 6.41 (br s, 1H), 5.61 (br s, 1H), 4.92 - 4.85 (m, 1H), 4.55 - 4.49

(m, 2H), 4.12 (q, J = 7.1 Hz, 3H), 2.88 (br t, J = 12.0 Hz, 2H), 2.40 - 2.09 (m, 5H), 1.94 - 1.82 (m, 2H), 1.77 - 1.68 (m, 2H), 1.50 - 1.47 (m, 9H), 1.42 - 1.40 (m, 9H).

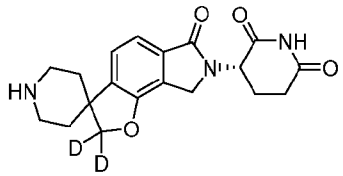
Step E: (3S)-3-(6-oxospiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl)piperidine-2,6-dione benzenesulfonate

[0361] The solution of anhydrous benzene sulfonic acid (19.6 g, 124 mmol, 2.00 eq) in MeCN (400 mL) was heated to 100 °C, before a solution of tert-butyl 7-[(1S)-4-tert-butoxy-1-carbamoyl-4-oxo-butyl]-6-oxo-spiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (47.0 g, 62.1 mmol, 1.00 eq, 70% purity) in MeCN (100 mL) was added dropwise to the mixture. The mixture was stirred at 100 °C for 12 hrs, before being cooled to 20 °C. The mixture was filtered, and the filter cake was dried under reduce pressure. The title compound (37.0 g) was obtained as a white solid, and the typical yield was 92.8%. ^{1}H NMR (400 MHz, D_2O-d_2) δ = 7.75 (br d, J = 7.4 Hz, 2H), 7.55 - 7.36 (m, 5H), 5.11 (br dd, J = 5.2, 13.4 Hz, 1H), 4.64 (s, 2H), 4.53 - 4.35 (m, 2H), 3.49 (br d, J = 13.2 Hz, 2H), 3.20 - 3.06 (m, 2H), 2.99 - 2.78 (m, 2H), 2.48 (dq, J = 5.3, 13.1 Hz, 1H), 2.25 - 2.08 (m, 3H), 2.05 - 1.93 (m, 5H).

Step F: (3S)-3-(6-oxospiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl)piperidine-2,6-dione hydrochloric acid

[0362] The solution of (3S)-3-(6-oxospiro[2,8-dihydrofuro[2,3-e]isoindole-3,4'-piperidine]-7-yl)piperidine-2,6-dione benzenesulfonate (37 g) in HCl/dioxane (4 M, 370 mL) was stirred at 20 °C for 12 hrs, before the mixture was filtered and the cake was washed with MeCN (2 x 200 mL). The filtered cake was dried under reduced pressure. The title compound (24.0 g) was obtained as a red solid, and the typical yield was 80.7%. ^{1}H NMR (400 MHz, D_2O-d_2) δ = 7.48 - 7.36 (m, 2H), 5.12 (dd, J = 5.3, 13.3 Hz, 1H), 4.69 - 4.61 (m, 2H), 4.53 - 4.37 (m, 2H), 3.51 (br dd, J = 3.4, 13.3 Hz, 2H), 3.22 - 3.06 (m, 2H), 2.98 - 2.80 (m, 2H), 2.56 - 2.43 (m, 1H), 2.29 - 2.08 (m, 3H), 2.05 - 1.90 (m, 2H).

Intermediate B3: (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl-2,2-d2)piperidine-2,6-dione



Step A: 1-(tert-butyl) 4-methyl 3,6-dihydropyridine-1,4(2H)-dicarboxylate

[0363] To a solution of tert-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate (10.0 g, 30.2 mmol, 1.0 eq) in MeOH (150.0 mL) were added DIPEA (39.0

g, 52.6 mL, 302 mmol, 10.0 eq) and $Pd(dppf)Cl_2$ (2.21 g, 3.02 mmol, 0.1 eq). The resulting mixture was stirred under CO (1 atm) at 70 °C for 1 h. After cooled to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with H_2O (30.0 mL) and extracted with EA (60 mL x 3). The organic layer was washed with brine (50 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate in petroleum ether, from 0% to 19%) to give 1-(tert-butyl) 4-methyl 3,6-dihydropyridine-1,4(2H)-dicarboxylate (5.80 g, yeild 79%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{12}H_{19}NO_4$, 241.29; m/z found, 186.7 $[M-55]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.86 (s, 1H), 4.00 (d, J = 2.4 Hz, 2H), 3.68 (s, 3H), 3.42 (t, J = 5.6 Hz, 2H), 2.28 - 2.25 (m, 2H), 1.41 (s, 9H).

Step B: tert-butyl 4-(hydroxymethyl-d2)-3,6-dihydropyridine-1(2H)-carboxylate

[0364] To a solution of 1-(tert-butyl) 4-methyl 3,6-dihydropyridine-1,4(2H)-dicarboxylate (2.10 g, 8.70 mmol, 1.0 eq) in anhydrous THF (50.0 mL) was added $LiAlD_4$ (402 mg, 9.57 mmol, 1.1 eq) at 0 °C in portions. The reaction mixture was stirred at 0 °C for 1 h. $Na_2SO_4 \cdot 10H_2O$ (5 g) was slowly added to above solution, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate in petroleum ether, from 0% to 70%) to give tert-butyl 4-(hydroxymethyl-d2)-3,6-dihydropyridine-1(2H)-carboxylate (700 mg, yield 37%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{11}H_{17}D_2NO_3$, 215.29; m/z found, no MS signal. ^1H NMR (400 MHz, DMSO-d_6) δ 5.56 (s, 1H), 4.71 (s, 1H), 3.80 (s, 2H), 3.39 (t, J = 5.6 Hz, 2H), 2.02 - 1.92 (m, 2H), 1.39 (s, 9H).

Step C: tert-butyl 4-(bromomethyl-d2)-3,6-dihydropyridine-1(2H)-carboxylate

[0365] To a solution of tert-butyl 4-(hydroxymethyl-d2)-3,6-dihydropyridine-1(2H)-carboxylate (1.90 g, 8.83 mmol, 1.0 eq) and Triphenylphosphine (3.47 g, 13.2 mmol, 1.5 eq) in DCM (50.00 mL) was added CBr_4 (4.39 g, 13.2 mmol, 1.5 eq) under N_2 in portions. The reaction mixture was stirred at 0 °C for 5 h. After evaporation, The residue was purified by flash column chromatography (ethyl acetate in petroleum ether, from 0% to 19%) to give tert-butyl 4-(bromomethyl-d2)-3,6-dihydropyridine-1(2H)-carboxylate (1.60 g, yield 65%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{11}H_{16}D_2BrNO_2$, 278.19; m/z found, 224.0 $[M-55]^+$.

Step D: tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl-d2)-3,6-dihydropyridine-1(2H)-carboxylate

[0366] A mixture of tert-butyl 4-(bromomethyl-d2)-3,6-dihydropyridine-1(2H)-carboxylate (2.00 g, 7.19 mmol, 1.0 eq), 5-bromo-4-hydroxyisobenzofuran-1(3H)-one (1.65 g, 7.19 mmol,

1.0 eq), and K_2CO_3 (1.99 g, 14.4 mmol, 2.0 eq) in DMF (30.0 mL) was stirred at 50 °C for 2 h. After cooled to room temperature, the mixture was dissolved in EA (100 mL), washed with brine (100 mL x 3), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate in petroleum ether, from 0% to 40%) to give tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl-d2)-3,6-dihydropyridine-1(2H)-carboxylate (2.30 g, yield 75%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{19}H_{20}D_2BrNO_5$, 426.30; m/z found, 450.1 $[M+Na]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 5.95 (s, 1H), 5.72 (s, 2H), 3.93 (s, 2H), 3.53 (t, J = 5.6 Hz, 2H), 2.28 (d, J = 1.8 Hz, 2H), 1.47 (s, 9H).

Step E: tert-butyl 6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate-2,2-d_2

[0367] To a solution of tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl-d2)-3,6-dihydropyridine-1(2H)-carboxylate (2.20 g, 5.16 mmol, 1.0 eq) and AIBN (254 mg, 1.55 mmol, 0.3 eq) in Toluene (30.0 mL) was added Tributyltin hydride (9.01 g, 8.38 mL, 31.0 mmol, 6.0 eq). The reaction mixture was stirred in a sealed tube at 120 °C for 16 h. After cooled to room temperature, the mixture was quenched by aqueous KF solution (30 mL) and the mixture was stirred for 2 h. After filtration, the filtrate was extracted with EA (50 mL x 3). The organic phase was washed with brine (30 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate in petroleum ether, from 0% to 33%) to give tert-butyl 6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate-2,2-d_2 (1.50 g, yield 83%) as a white solid. LC-MS (ESI): mass calcd. for $C_{19}H_{21}D_2NO_5$, 347.41; m/z found, 292.2 $[M-55]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 5.36 (s, 2H), 3.95 (d, J = 12.2 Hz, 2H), 2.91 - 2.87 (s, 2H), 1.85 - 1.77 (m, 2H), 1.71 - 1.67 (m, 2H), 1.42 (s, 9H).

Step F: 1'-(tert-butoxycarbonyl)-7-(hydroxymethyl)-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic-2,2-d_2 acid

[0368] To a solution of tert-butyl 6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate-2,2-d_2 (600 mg, 1.73 mmol, 1.0 eq) in THF (12.0 mL), MeOH (12.0 mL), and H_2O (4.00 mL) was added NaOH (138 mg, 3.45 mmol, 2.0 eq). The reaction mixture was stirred at 40 °C for 1 h. After cooled to room temperature, the reaction mixture was diluted with EA (40 mL), adjusted to pH = 4-5 with aqueous HCl solution (3 *N*), and extracted with EA (50 mL x 4). The organic layer was washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to 1'-(tert-butoxycarbonyl)-7-(hydroxymethyl)-

2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic-2,2-d_2 acid (600 mg, yield 95%) as a colorless oil. The crude product was directly used in the next step without purification. LC-MS (ESI): mass calcd. for $C_{19}H_{23}D_2NO_6$, 365.42; m/z found, 364.3 $[M-H]^-$.

Step G: tert-butyl 8-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate-2,2-d_2

[0369] To a solution of 1'-(tert-butoxycarbonyl)-7-(hydroxymethyl)-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic-2,2-d_2 acid (1.50 g, 4.10 mmol, 1.0 eq) in DCM (20.0 mL) was added active manganese dioxide (7.14 g, 82.1 mmol, 20.0 eq) at 25 °C. the reaction mixture was stirred at 25 °C for 4 h. After filtration via a short silica gel column, the filtrate is collected and concentrated under reduced pressure to tert-butyl 8-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate-2,2-d_2 (760 mg, yield 52%) as a colorless oil. The crude product was directly used in next step without purification. LC-MS (ESI): mass calcd. for $C_{19}H_{21}D_2NO_6$, 363.41; m/z found, 364.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 6.65 (s, 1H), 3.95 (d, J = 12.2 Hz, 2H), 2.89 (s, 2H), 1.83 - 1.78 (m, 2H), 1.70 - 1.67 (m, 2H), 1.43 (s, 9H).

Step H: tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate-2,2-d_2

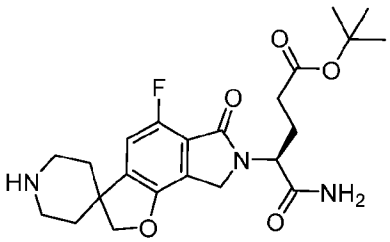
[0370] To a solution of tert-butyl 8-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate-2,2-d_2 (350 mg, 963 μmol, 1.0 eq) and tert-butyl (S)-4,5-diamino-5-oxopentanoate hydrochloride (460 mg, 1.93 mmol, 2.0 eq) in DMF (10.0 mL) was added Acetic acid (578 mg, 554 μL, 9.63 mmol, 10.0 eq). The reaction mixture was stirred at 40 °C for 2 h, then Sodium triacetoxyborohydride (4.08 g, 19.3 mmol, 20.0 eq). The mixture was stirred at 40 °C for 16 h. After cooled to room temperature, the mixture was dissolved in EA (40 mL), washed with brine (30 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 90%) to afford tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate-2,2-d_2 (300 mg, yield 58%) as a white solid. LC-MS (ESI): mass calcd. for $C_{28}H_{37}D_2N_3O_7$, 531.65; m/z found, 532.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.23 (s, 1H), 4.77 - 4.73 (m, 1H), 4.56 (d, J = 17.2 Hz, 1H), 4.45 (d, J = 17.2 Hz, 1H), 4.00 (d, J = 12.8 Hz, 2H), 2.96 (s, 2H), 2.23 - 2.20 (m, 3H), 2.09 - 2.02 (m, 1H), 1.97 - 1.84 (m, 2H), 1.82 - 1.74 (m, 2H), 1.49 (s, 9H), 1.38 (s, 9H).

Step I: (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl-2,2-

d2)piperidine-2,6-dione benzenesulfonate

[0371] To a solution of tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate-2,2-d_2 (350 mg, 660 μmol, 1.0 eq) in MeCN (10.0 mL) was added anhydrous benzenesulfonic acid (313 mg, 1.98 mmol, 3.0 eq) and the reaction mixture was stirred at 90 °C for 7 h. After cooled to room temperature, the mixture was concentrated under reduced pressure and the residue was slurred with acetonitrile (10 mL) to afford (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl-2,2-d2)piperidine-2,6-dione benzenesulfonate (300 mg, yield 88%) as a yellow solid. The crude product was directly used in next step without further purification. LC-MS (ESI): mass calcd. for $C_{25}H_{25}D_2N_3O_7S$, 515.58; m/z found, 358.3 $[M+H]^+$.

Intermediate B4: tert-butyl (S)-5-amino-4-(5-fluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)-5-oxopentanoate



Step A: 4-bromo-2-fluoro-5-hydroxybenzoic acid

[0372] To a solution of compound 2-fluoro-5-hydroxybenzoic acid (10.0 g, 1.0 eq.) in MeCN (100 mL) was added TsOH (10.1 g, 1.0 eq.) at rt. The mixture was stirred for 10 min, then added NBS (11.4 g, 1.1 eq.) in MeCN (50 mL) via dropwise during 20 min. The reaction mixture was stirred overnight at rt, and concentrated to afford the title compound (15.0 g) as a crude, which was used in next step without further purification.

Step B: methyl 4-bromo-2-fluoro-5-hydroxybenzoate

[0373] To a solution of 4-bromo-2-fluoro-5-hydroxybenzoic acid (crude, 15.0 g, 1.0 eq.) in MeOH (100 mL) was added 2,2-Dimethoxypropane (18.3 g, 3.0 eq.) at rt. The reaction mixture was stirred overnight at 60 °C. After cooled to room temperature and concentrated. The residual was purified by flash column chromatography (PE/EA) to afford the title compound (600 mg).

Step C: methyl 4-bromo-6-fluoro-2-formyl-3-hydroxybenzoate

[0374] To a solution of methyl 4-bromo-2-fluoro-5-hydroxybenzoate (249 mg, 1 mmol, 1 eq.) in TFA (5 mL) was added HMTA (560 mg, 4 mmol, 4 eq) at 20 °C. The mixture was stirred at 125 °C for 12 h. TLC (Petroleum ether/Ethyl acetate = 5/1) indicated starting materials was consumed completely and there was desired product. The mixture was quenched with 2N HCl

(5 V) and a yellow solid formed. The mixture was stirred for 10 min and then additional water (5 V) was added and stirred for 1 h. The mixture was filtered. The filter cake was dissolved in DCM and filtered on celite, dried and then remove most of the solvent in vacuo. The title compound (110 mg, 0.4 mmol, 40% yield) was obtained as a gray solid.

[0375] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.28 (s, 1H), 10.08 (s, 1H), 7.65 (d, J = 8.7 Hz, 1H), 4.01 (s, 3H). LC- MS (m/z): $[M - H]^+$ = 274.99.

Step D: tert-butyl (S)-5-amino-4-(5-bromo-7-fluoro-4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate

[0376] tert-Butyl (*S*)-4,5-diamino-5-oxopentanoate (212 mg, 1.05 mmol, 1.05 eq, HCl) was added in MeOH (5 mL) at 20 °C. Then DIEA (1.05 mmol, 1.05 eq), methyl 4-bromo-6-fluoro-2-formyl-3-hydroxybenzoate (277 mg,1 mmol, 1 eq) and AcOH (1.5 mmol, 1.5 eq) were added to the mixture at the same temperature. After 1.5 h, $NaBH_3CN$ (2 mmol, 2 eq) was added to the mixture in portions and stirred the mixture at 20 °C for 3 h. After the reaction completed, the reaction mixture was quenched by addition H_2O at 20 °C, and then concentrated under reduced pressure to remove MeOH. Then the mixture was extracted with EtOAc. The combined organic layers were washed with brine (200 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/1 to Ethyl acetate). The title compound (293 mg, 0.68 mmol, 65% yield) was obtained as a yellow solid.

Step E: benzyl (S)-4-(((2-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-6-fluoro-1-oxoisoindolin-4-yl)oxy)methyl)-3,6-dihydropyridine-1(2H)-carboxylate

[0377] tert-Butyl (S)-5-amino-4-(5-bromo-7-fluoro-4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate (202 mg, 0.47 mmol, 1 eq), benzyl 4-(chloromethyl)-3,6-dihydropyridine-1(2H)-carboxylate (280 mg, 0.49 mmol, 1.05 eq) and K_2CO_3 (194 mg, 1.41 mmol, 3 eq) were added in DMF (5 mL) at 20 °C. Then the mixture was stirred at 60 °C for 12 h. After the reaction completed, the mixture was concentrated under reduced pressure to give a residue, which was added water (20 mL). The product was extracted with DCM (20 mL x 3). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel to afford the title compound as a yellow solid (194 mg, 60% yield).

Step F: benzyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-fluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

[0378] Benzyl (S)-4-(((2-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-6-fluoro-1-oxoisoindolin-4-yl)oxy)methyl)-3,6-dihydropyridine-1(2H)-carboxylate (330 mg, 0.5 mmol,

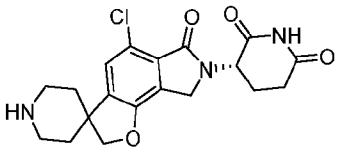
1 eq), Bu_3SnH (614 mg, 2 mmol) and AIBN (8.2 mg, 0.05 mmol, 0.1 eq) were added in toluene (5 mL) at 20 °C and then stirred the mixture at 110 °C for 12 h. After the reaction completed, the mixture was quenched by addition saturated potassium fluoride solution and stirred for 1h. The product was extracted with EA. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel to afford the title compound as a yellow solid (84 mg, 29% yield).

[0379] ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 5H), 6.84 (d, J = 8.4 Hz, 1H), 6.40 (s, 1H), 5.35 (s, 1H), 5.16 (s, 2H), 4.85 (dd, J = 8.9, 6.1 Hz, 1H), 4.52 (s, 2H), 4.48 (d, J = 17.2 Hz, 1H), 4.36 (d, J = 17.2 Hz, 1H), 4.20 (brs, 2H), 4.12 (q, J = 7.1 Hz, 1H), 2.94 (m, 2H), 2.37-2.16 (m, 6H), 1.76 (m, 2H), 1.42 (s, 9H).

Step G: tert-butyl (S)-5-amino-4-(5-fluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)-5-oxopentanoate

[0380] To a 100 mL flask equipped with a magnetic stirring bar was added benzyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-fluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (200 mg), MeOH (10 mL), and then added 10% Pd/C (20 mg) . Followed by flushing flask with hydrogen, a balloon with hydrogen was attached and the reaction mixture was stirred for 2 h. Upon full consumption of the starting material by TLC monitoring (DCM:MeOH =10:1), the reaction mixture was filtered through celite and washed through with additional MeOH. Solvent was removed and the residual title compound (120 mg,) as a white solid was used directly in the next step.

Intermediate B5: (S)-3-(5-chloro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



Step A: tert-butyl (S)-7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

[0381] To a mixture of (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (100 mg, 0.28 mmol, 1.0 eq) and TEA (85 mg, 0.84 mmol, 3 eq) in dry DCM (10 mL) was slowly added Di-tert-butyl dicarbonate (123 mg, 0.56 mmol, 2.0 eq). The mixture was stirred under N_2 atmosphere at room temperature for 5 h. The reaction mixture was quenched with water (10 mL) and exacted with EtOAc (15 mL x 3). The organic

layer was washed with brine (20 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 (ethyl acetate in petroleum ether, from 0% to 50%) to afford tert-butyl (S)-7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (120 mg, yield 94%) as a light yellow solid. LC-MS (ESI): mass calcd for C24H29N3O6: 455; m/z found, 456.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 5.11 - 5.06 (m, 1H), 4.65 - 4.50 (m, 2H), 4.39 (d, J = 17.2 Hz, 1H), 4.22 (d, J = 17.2 Hz, 1H), 3.94 (d, J = 11.2 Hz, 2H), 3.07 - 2.76 (m, 3H), 2.62 - 2.56 (m, 1H), 2.42 - 2.33 (m, 1H), 2.05 - 1.91 (m, 1H), 1.88 - 1.76 (m, 2H), 1.70 (d, J = 10.6 Hz, 2H), 1.43 (s, 9H).

Step B: tert-butyl (S)-5-chloro-7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

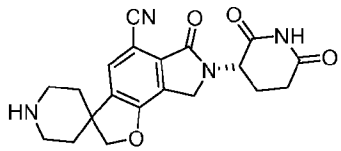
[0382] To a solution of tert-butyl (S)-7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (60 mg, 132 μmol, 1.0 eq) in dry ACN (5.0 mL) was added NCS (18 mg, 132 μmol, 1.0 eq) and the mixture was stirred under N_2 atmosphere at room temperature for 6 h. The reaction mixture was quenched with water (10 mL) and exacted with EtOAc (15 mL x 3). The organic layer was washed with brine (20 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 (ethyl acetate in petroleum ether, from 0% to 50%) to afford tert-butyl (S)-4-chloro-7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (60.0 mg, yield 93%) as a light yellow solid. LC-MS (ESI): mass calcd for $C_{24}H_{28}ClN_3O_6$ 489; m/z found, 490.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 7.62 (s, 1H), 5.20 - 5.15 (m, 1H), 4.80 - 4.67 (m, 1H), 4.47 (d, J = 17.4 Hz, 1H), 4.30 (d, J = 17.4 Hz, 1H), 4.15 - 4.05 (m, 2H), 3.10 - 2.91 (m, 3H), 2.65 - 2.611 (m, 1H), 2.53 - 2.45 (m, 1H), 2.11 - 2.06 (m, 1H), 2.03 - 1.94 (m, 2H), 1.86 - 1.75 (m, 2H), 1.56 (s, 9H).

Step C: (S)-3-(5-chloro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

[0383] To a solution of tert-butyl (S)-7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (50 mg, 110 μmol, 1.0 eq) in EA (5.0 mL) was added HCl-dioxane (4 *N*) (0.25 mL, 1.00 mmol, 10.0 eq) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure to afford (S)-3-(4-chloro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione hydrochloride (40.0 mg, yield 93%) as a light yellow solid. LC-MS

(ESI): mass calced for $C_{19}H_{20}ClN_3O_4$ 389; m/z found, 390.2 $[M+H]^+$.

Intermediate B6: (S)-7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-5-carbonitrile



Step A: (S)-tert-butyl 7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-cyano-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

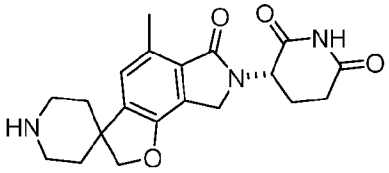
[0384] To a solution of tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (200 mg, 329 μmol, 1.0 eq) in DMF (10.0 mL) was added cuprous cyanide (88.3 mg, 986 μmol, 3.0 eq) at 25 °C. The reaction mixture was stirred at 140 °C for 5 h. After cooled to room temperature, the reaction mixture was quenched with water (20 mL) and extracted with DCM (30 mL x 3). The organic layer was washed with brine (30 mL x 4), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/EA = 1/1) to give (S)-tert-butyl 7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-cyano-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (160 mg, yield 88%) as a yellow solid. LC-MS (ESI): mass calced for: $C_{29}H_{38}N_4O_7$ 554.27; m/z found, 555.3 $[M+H]^+$.

Step B: (S)-7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-5-carbonitrile

[0385] To a solution of (S)-tert-butyl 7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-cyano-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (160 mg, 288 μmol, 1.0 eq) in MeCN (5.0 mL) was added anhydrous benzenesulfonic acid (151.4 mg, 288 μmol, 3.0 eq) at 0 °C. The reaction mixture was stirred at 80 °C for 3 h. The reaction mixture was concentrated under reduced pressure to get crude (S)-7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-5-carbonitrile (20.0 mg, yield 18%) as a yellow solid. The crude product was directly used in next step without further purification. LC-MS (ESI): mass calced for: $C_{20}H_{20}N_4O_4$ 380.15; m/z found, 381.2 $[M+H]^+$.

Intermediate B7: (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-

3,4'-piperidin]-7-yl)piperidine-2,6-dione



Step A: tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

[0386] To a solution of tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (200 mg, 378 μmol, 1.0 eq) in MeCN (5.0 mL) was added NBS (67.2 mg, 378 μmol, 1.0 eq) at 25 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with water (10 mL) and extracted with EA (10 mL x 3). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/EA = 2/1) to give tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (180 mg, yield 78%) as a white solid. LC-MS (ESI): mass calced for: $C_{28}H_{38}BrN_3O_7$ 607.2; m/z found, 608.2 $[M+H]^+$.

Step B: tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-methyl-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

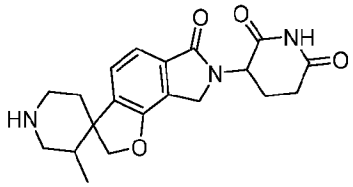
[0387] To a solution of tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (200 mg, 329 μmol, 1.0 eq), Potassium carbonate (136 mg, 986 μmol, 3.0 eq), and $Pd(dppf)Cl_2$ (48.1 mg, 65.7 μmol, 0.2 eq) in 1,4-dioxane (5.0 mL) and water (0.5 mL) was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (82.5 mg, 657 μmol, 2.0 eq) at 25 °C. The reaction mixture was stirred under N_2 at 80 °C for 2 h. After cooled to room temperature, the reaction mixture was filtered and the filtrate was diluted with water (10 mL), and extracted with EtOAc (10 mL x 3). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA = 1/1) to afford tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-methyl-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (141 mg, yield 79%) as a yellow solid. LC-MS (ESI): mass calced for: $C_{29}H_{41}N_3O_7$ 543.3; m/z found, 544.3 $[M+H]^+$.

Step C: (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

[0388] To a solution of tert-butyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-

methyl-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (141 mg, 259 μmol, 1.0 eq) in MeCN (5.0 mL) was added benzenesulfonic acid (123 mg, 778 μmol, 3.0 eq) at 25 °C. The reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure to get (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione benzenesulfonic acid (360 mg, yield 79%, 30% purity) as a yello oil. The crude product was directly used in next step without further purification. LC-MS (ESI): mass calced for: $C_{20}H_{23}N_3O_4$ 369.2; m/z found, 370.2 $[M+H]^+$.

Intermediate B8: 3-(3'-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



Step A: tert-butyl 4-methyl-1-oxa-6-azaspiro[2.5]octane-6-carboxylate

[0389] To a solution of Trimethyl(oxo)sulfonium iodide (8.25 g, 37.5 mmol, 4.0 eq) in DMSO (10.0 mL) was added NaH (60% suspend in oil) (1.5 g, 37.5 mmol, 4.0 eq) at 0 °C and the mixture was stirred under N_2 at room temperature for 1 h. Then tert-butyl 3-methyl-4-oxopiperidine-1-carboxylate (2.00 g, 9.38 mmol, 1.0 eq) was added to above mixture and the resulting mixture was stirred under N_2 at room temperature for 16 h. The reaction mixture was quenched with ice-water (50 mL) and exacted with EA (100 mL x 3). The organic layer was washed with brine (100 mL x 4), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 20% to 50%) to afford tert-butyl 4-methyl-1-oxa-6-azaspiro[2.5]octane-6-carboxylate (400 mg, yield 19%) as a light yellow solid. LC-MS (ESI): mass calcd. for $C_{12}H_{21}NO_3$, 227.30; m/z found, 172.1 $[M-55]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 3.48 - 3.40 (m, 3H), 3.14 (s, 1H), 2.75 (d, J = 4.6 Hz, 1H), 2.55 (dd, J = 12.0, 8.6 Hz, 1H), 1.73 (s, 1H), 1.52 (s, 2H), 1.41 (s, 9H), 0.75 (d, J = 6.8 Hz, 3H).

Step B: tert-butyl 4-(hydroxymethyl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate

[0390] To a solution of tert-butyl 4-methyl-1-oxa-6-azaspiro[2.5]octane-6-carboxylate (1.00 g, 4.40 mmol, 1.0 eq) in Toluene (10.0 mL) was added Aluminum isopropoxide (2.70 g, 2.60 mL, 13.2 mmol, 3.0 eq). The mixture was stirred under N_2 at 110 °C for 16 h . After cooled to room temperature, the reaction mixture was adjusted to pH = 4-5 with aqueous HCl solution

(3 *N*) and exacted with EA (50 mL x 3). The organic layer was washed with brine (20 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 (ethyl acetate in petroleum ether, from 20% to 50%) to afford tert-butyl 4-(hydroxymethyl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate (850 mg, yield 85%) as a light yellow oil. LC-MS: No MS signal under routine condition. LC-MS (ESI): mass calcd. for $C_{12}H_{21}NO_3$, 227.30; m/z found, no MS signal.

Step C: tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate

[0391] To a solution of 5-bromo-4-hydroxyisobenzofuran-1(3H)-one (420 mg, 1.83 mmol, 1.0 eq) in THF (20.0 mL) were added Triphenylphosphine (721 mg, 2.75 mmol, 1.5 eq) and tert-butyl 4-(hydroxymethyl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate (417 mg, 1.83 mmol, 1.0 eq). The mixture was stirred under N_2 at 0 °C for 20 min, then DIAD (556 mg, 535 μL, 2.75 mmol, 1.5 eq) was dropwise to above mixture. The resulting mixture was stirred at room temprature overnight. After evaporation, the crude product was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 20%) to afford tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate (180 mg, yield 22%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{20}H_{24}BrNO_5$, 438.32; m/z found, 342.0 $[M-55]^+$.

Step D: tert-butyl 3'-methyl-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate

[0392] To a solution of tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)-3-methyl-3,6-dihydropyridine-1(2H)-carboxylate (180 mg, 411 μmol, 1.0 eq) and AIBN (13.5 mg, 82.1 μmol, 0.2 eq) in Toluene (20.0 mL) was added Tributyltin hydride (478 mg, 444 μL, 1.64 mmol, 4.0 eq). The reaction was stirred under N_2 at 110 °C for 16 h. After cooled to room temperature, the mixture was quenched by saturated aqueous KF solution (30 mL) and stirred for 1 h. The reaction mixture was extracted with EA (30 mL x 3). The organic phases were combined, washed with brine (30 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The mixture was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 30%) to give tert-butyl 3'-methyl-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (120 mg, yield 81%) as a white solid. LC-MS (ESI): mass calcd. for $C_{20}H_{25}NO_5$, 359.42; m/z found, 304.0 $[M-55]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.47 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 5.36 (d, J = 2.4 Hz, 2H), 4.79 (d, J = 9.8 Hz, 1H), 4.48 (d, J = 9.8 Hz, 1H), 3.99 - 3.77 (m, 2H), 3.04 - 2.66 (m, 2H), 2.01 (d, J = 10.8 Hz, 3H), 1.97 - 1.87 (m, 2H),

1.77 (d, J = 13.2 Hz, 1H), 1.43 (s, 9H).

Step E: tert-butyl 3'-methyl-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate

[0393] To a solution of tert-butyl 3'-methyl-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (110 mg, 306 μmol, 1.0 eq) in in THF (9.00 mL), MeOH (9.00 mL), and H_2O (3.00 mL) was added NaOH (24 mg, 612 μmol, 2.0 eq). The reaction mixture was stirred at 40 °C for 1 h. After cooled to room temperature, the reaction mixture was diluted with EA (20 mL), adjusted to pH = 4-5 with aqueous HCl solution (3 *N*), and extracted with EA (40 mL x 4). The organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to get tert-butyl 3'-methyl-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (110 mg, yield 90%) as a colorless oil. The crude product was directly used in next step without purification. LC-MS (ESI): mass calcd. for $C_{20}H_{27}NO_6$, 377.44; m/z found, 376.4 $[M-H]^-$.

Step F: 1'-(tert-butoxycarbonyl)-7-formyl-3'-methyl-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid

[0394] A mixture of 1'-(tert-butoxycarbonyl)-7-(hydroxymethyl)-3'-methyl-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (110 mg, 291 μmol, 1.0 eq) and active Manganese dioxide (507 mg, 5.83 mmol, 20.0 eq) in DCM (20.0 mL) was stirred at room temperature for 16 h. After filtration via a short column, the filtrate is collected and concentrated under reduced pressure to afford 1'-(tert-butoxycarbonyl)-7-formyl-3'-methyl-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (100 mg, yield 91%) as a colorless oil. The crude product was directly used in next step without purification. LC-MS (ESI): mass calcd. for $C_{20}H_{25}NO_6$, 375.42; m/z found, 376.1 $[M+H]^+$.

Step G: tert-butyl 7-(2,6-dioxopiperidin-3-yl)-3'-methyl-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

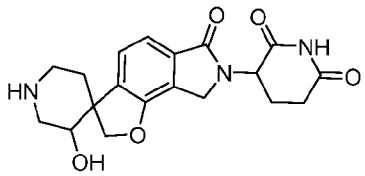
[0395] To a solution of 1'-(tert-butoxycarbonyl)-7-formyl-3'-methyl-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (110 mg, 293 μmol, 1.0 eq) and 3-aminopiperidine-2,6-dione hydrochloride (96.5 mg, 586 μmol, 2.0 eq) in DMF (10.0 mL) was added Acetic acid (0.52 g, 0.50 mL, 8.7 mmol, 30.0 eq) and the reaction mixture was stirred at 40 °C for 2 h. Then Sodium triacetoxyborohydride (186 mg, 879 μmol, 3.0 eq) was added to above mixture and the mixture was stirred at 40 °C for 16 h. After cooled to room temperature, the mixture was dissolve in EA (40 mL), washed with brine (30 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH = 10/1) to afford tert-butyl 7-(2,6-dioxopiperidin-3-yl)-3'-methyl-6-

oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (80.0 mg, yield 58%) as a gray solid. LC-MS (ESI): mass calcd. for $C_{25}H_{31}N_3O_6$, 469.54; m/z found, 470.2 $[M+H]^+$.

Step H: 3-(3'-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

[0396] To a solution of tert-butyl 7-(2,6-dioxopiperidin-3-yl)-3'-methyl-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (70.0 mg, 149 μmol, 1.0 eq) in DCM (3 mL) was added dropwise HCl-dioxane (4 *N*) (8.0 mL, 32 mmol, 10.4 eq) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give 3-(3'-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione hydrochloride (30.0 mg, yield 54%) as a gray solid. The crude product was directly used in next step without further purification. LC-MS (ESI): mass calcd. for $C_{20}H_{23}N_3O_4$, 369.42; m/z found, 370.1 $[M+H]^+$.

Intermediate B9: 3-(3'-hydroxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



Step A: 1'-(tert-butoxycarbonyl)-3'-hydroxy-7-(hydroxymethyl)-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid

[0397] To a mixture of tert-butyl 3'-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (400 mg, 1.11 mmol, 1.0 eq) in THF (9.00 mL), MeOH (9.00 mL), and H_2O (3.00 mL) was added NaOH (89 mg, 2.21 mmol, 2.0 eq) and the reaction mixture was stirred at 40 °C for 1 h. After cooled to room temperature, the reaction mixture was diluted with EA (20 mL), adjusted to pH = 4-5 with aqueous HCl solution (3 *N*), and extracted with EA (40 mL x 4). The organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to provide 1'-(tert-butoxycarbonyl)-3'-hydroxy-7-(hydroxymethyl)-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (400 mg, yield 95%) as a colorless oil. The crude product was directly used in next step without purification. LC-MS (ESI): mass calcd. for $C_{19}H_{25}NO_7$, 379.41; m/z found, 378.3 $[M-H]^-$.

Step B: 1'-(tert-butoxycarbonyl)-7-formyl-3'-hydroxy-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid

[0398] A mixture of 1'-(tert-butoxycarbonyl)-3'-hydroxy-7-(hydroxymethyl)-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (420 mg, 1.11 mmol, 1.0 eq) and active manganese dioxide (1.92 g, 22.1 mmol, 20.0 eq) in DCM (40.0 mL) was stirred at room temperature for 16 h. After filtration via a short column, the filtrate was collected and concentrated under reduced pressure to 1'-(tert-butoxycarbonyl)-7-formyl-3'-hydroxy-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (260 mg, yield 62%) as a colorless oil. The crude product was directly used in next step without purification. LC-MS (ESI): mass calcd. for $C_{19}H_{21}F_2NO_6$, 377.39; m/z found, 378.1 $[M+H]^+$.

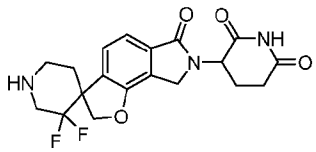
Step C: tert-butyl 7-(2,6-dioxopiperidin-3-yl)-3'-hydroxy-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

[0399] To a solution of 1'-(tert-butoxycarbonyl)-7-formyl-3'-hydroxy-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (260 mg, 689 μmol, 1.0 eq) and 3-aminopiperidine-2,6-dione hydrochloride (227 mg, 1.38 mmol, 2.0 eq) in DMF (10.0 mL) was added Acetic acid (1.0 mL) and the reaction mixture was stirred at 40 °C for 2 h. Sodium triacetoxyborohydride (438 mg, 2.07 mmol, 3.0 eq) was added to above mixture and the resulting mixture was stirred at 40 °C for 16 h. After cooled to room temperature, the mixture was dissolve in EA (40 mL), washed with brine (30 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (MeOH in DCM, 10%) to afford tert-butyl 7-(2,6-dioxopiperidin-3-yl)-3'-hydroxy-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (260 mg, yield 80%) as a grey solid. LC-MS (ESI): mass calcd. for $C_{24}H_{29}N_3O_7$, 471.51; m/z found, 472.2 $[M+H]^+$.

Step D: 3-(3'-hydroxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

[0400] To a solution of tert-butyl 7-(2,6-dioxopiperidin-3-yl)-3'-hydroxy-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (260 mg, 551 μmol, 1.0 eq) in DCM (5.0 mL) was added TFA (1.7 mL, 22.1 mmol, 40.0 eq) and the reaction mixture was stirred at room temperature for 6 h. The mixture was cautiously concentrated under reduced pressure to afford 3-(3'-hydroxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione trifluoroacetate (100 mg, yield 48%) as a yellow oil. The crude product was directly used in next step without further purification. LC-MS (ESI): mass calcd. for $C_{19}H_{21}N_3O_5$, 371.39; m/z found, 372.2 $[M+H]^+$.

Intermediate B10. 3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



Step A: tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)-3,6-dihydropyridine-1(2H)-carboxylate

[0401] To a solution of 5-bromo-4-hydroxyisobenzofuran-1(3H)-one (5.0 g, 21.80 mmol, 1.0 eq) in THF (150 mL) were added tert-butyl- 4-(hydroxymethyl)-3,6-dihydropyridine-1(2H)-carboxylate (5.59 g, 26.2 mmol, 1.2 eq) and Triphenylphosphine (8.59 g, 32.7 mmol, 7.31 mL, 1.5 eq). The mixture was stirred under N_2at 0 °C for 20 min. Then DIAD (6.62 g, 32.7 mmol, 6.37 mL, 1.5 eq) was dropwise added to above mixture and the mixture was stirred at room temperature overnight. After evaporation, the crude product was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 20%) to afford tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)-3,6-dihydropyridine-1(2H)-carboxylate (9.0 g, yield 97%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{19}H_{22}BrNO_5$, 424.29; m/z found, 369.9 $[M+H-56]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 5.89 (s, 1H), 5.66 (s, 2H), 4.66 (s, 2H), 3.88 (s, 2H), 3.48 (dd, J = 14.6, 9.0 Hz, 2H), 2.22 (s, 2H), 1.41 (s, 9H).

Step B: tert-butyl 6-oxo-2',3',6,8-tetrahydro-1'H,2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-pyridine]-1'-carboxylate

[0402] To a solution of tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)-3,6-dihydropyridine-1(2H)-carboxylate (5.00 g, 7.90 mmol, 1.0 eq) in DMF (30.0 mL) were added sodium formate (591 mg, 8.69 mmol, 1.1 eq), palladium diacetate (177 mg, 790 μmol, 0.1 eq), sodium acetate (1.62 g, 19.7 mmol, 2.5 eq), and TEA (1.44 g, 8.69 mmol, 1.33 mL, 1.1 eq). The mixture was stirred under N_2 at 70 °C for 16 h. After cooled to room temperature, the mixture was filtered and the cake was washed with EA (100 mL). The filtrate was washed with brine (60 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 30%) to afford tert-butyl 6-oxo-2',3',6,8-tetrahydro-1'H,2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-pyridine]-1'-carboxylate (1.70 g, yield 62.7%) as a colorless oil. LC-MS (ESI): mass calcd. for $C_{19}H_{21}NO_5$,

343.38; m/z found, 344.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.41 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.03 - 6.98 (m, 1H), 5.38 (s, 2H), 4.88 - 4.82 (m, 1H), 4.60 (d, J = 9.2 Hz, 1H), 4.39 (d, J = 9.2 Hz, 1H), 3.81 - 3.75 (m, 1H), 3.47 - 3.41 (m, 1H), 2.02 - 1.98 (m, 1H), 1.84 - 1.78 (m, 1H), 1.47 (s, 9H).

Step C: tert-butyl 3'-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate

[0403] To a solution of tert-butyl 6-oxo-2',3',6,8-tetrahydro-1'H,2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-pyridine]-1'-carboxylate (4.70 g, 13.7 mmol, 1.0 eq) in THF (60.0 mL) was added BH_3-THF (1 *N*) (34.2 mL, 34.2 mmol, 2.5 eq) under N_2 at -78 °C. The reaction was allowed to slowly warm to 0 °C and stirred at 0 °C for 5 h. Water (5 mL) was added to above mixture, followed by Sodium perborate (5.60 g, 68.4 mmol, 5.0 eq). The resulting mixture was stirred overnight. The mixture was diluted with DCM (100 mL), washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 40%) to afforded tert-butyl 3'-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (2.70 g, yield 54%) as a white powder. LC-MS (ESI): mass calcd. for $C_{19}H_{23}NO_6$, 361.39; m/z found, 306.1 $[M+H-56]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 5.35 (d, J = 2.6 Hz, 2H), 5.31 (d, J = 4.6 Hz, 1H), 4.83 (d, J = 9.0 Hz, 1H), 4.53 (d, J = 9.0 Hz, 1H), 4.01 (s, 1H), 3.87 (s, 1H), 3.76 - 3.73 (m, 1H), 2.83 - 2.56 (m, 2H), 1.88 - 1.74 (m, 2H), 1.43 (s, 9H).

Step D: tert-butyl 3',6-dioxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate

[0404] To a solution of tert-butyl 3'-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (1.80 g, 4.98 mmol, 1.0 eq) in DCM (30.0 mL) was added Dess-Martin Periodinane (5.28 g, 12.5 mmol, 2.5 eq). The mixture was stirred at room temperature for 4 h. The reaction was diluted with DCM (60 mL), washed with aqueous sodium thiosulfate solution (30 mL x 2) and washed with brine (40 mL x 2). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 40%) to afford tert-butyl 3',6-dioxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (1.3 g, yield 72.6%) as a colorless oil. LC-MS (ESI): mass calcd. for $C_{19}H_{21}NO_6$, 359.38; m/z found, 360.1 $[M+H]^+$.

Step E: tert-butyl 3',6-dioxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate

[0405] To a solution of tert-butyl 3',6-dioxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (1.20 g, 3.34 mmol, 1.0 eq), triethylammonium fluoride (3.23 g, 3.27 mL, 20.0 mmol, 6.0 eq), and N,N-diethyl-S,S-difluoro-sulfiliminium tetrafluoroborate (3.44 g, 15.0 mmol, 4.5 eq) in DCM (50.0 mL) was added TEA (845 mg, 1.16 mL, 8.35 mmol, 2.5 eq) at 25 °C and the mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and extracted with DCM (30 mL x 3). The separated organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 30%) to afford tert-butyl 3',3'-difluoro-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (260 mg, yield 20%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{19}H_{21}F_2NO_5$, 381.38; m/z found, 382.1 $[M+H]^+$.

Step F: 1'-(tert-butoxycarbonyl)-3',3'-difluoro-7-(hydroxymethyl)-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid

[0406] To a solution of tert-butyl 3',3'-difluoro-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (280 mg, 734 μmol, 1.0 eq) in THF (9.00 mL), MeOH (9.00 mL), and H_2O (3.00 mL) was added NaOH (44 mg, 1.10 mmol, 1.5 eq). The mixture was stirred at 40 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with EA (20 mL), adjusted to pH = 4-5 with aqueous HCl solution (3 *N*), and extracted with EA (40 mL x 4). The organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to 1'-(tert-butoxycarbonyl)-3',3'-difluoro-7-(hydroxymethyl)-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (290 mg, yield 99%) as a colorless oil. The crude product was directly used in next step without purification. LC-MS (ESI): mass calcd. for $C_{19}H_{23}F_2NO_6$, 399.39; m/z found, 398.3 $[M-H]^-$.

Step G: 1'-(tert-butoxycarbonyl)-3',3'-difluoro-7-formyl-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid

[0407] A solution of 1'-(tert-butoxycarbonyl)-3',3'-difluoro-7-(hydroxymethyl)-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (260 mg, 651 μmol, 1.0 eq) and active Manganese dioxide (1.13 g, 13.0 mmol, 20.0 eq) in DCM (20.0 mL) was stirred at room temperature for 16 h. After filtration via a short column, the filtrate is collected and concentrated under reduced pressure to 1'-(tert-butoxycarbonyl)-3',3'-difluoro-7-formyl-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (250 mg, yield 96.6%) as a colorless oil. The crude product was directly used in next step without purification. LC-MS (ESI): mass calcd. for $C_{19}H_{21}F_2NO_6$, 397.37; m/z found, 398.1 $[M+H]^+$.

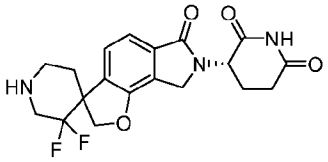
Step H: tert-butyl 7-(2,6-dioxopiperidin-3-yl)-3',3'-difluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

[0408] To a solution of 1'-(tert-butoxycarbonyl)-3',3'-difluoro-7-formyl-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (260 mg, 654 μmol, 1.0 eq) and 3-aminopiperidine-2,6-dione hydrochloride (215 mg, 1.31 mmol, 2.0 eq) in DMF (10.0 mL) was added Acetic acid (0.52 g, 0.50 mL, 8.7 mmol, 13.0 eq) and the reaction was stirred at 40 °C for 2 h. Sodium triacetoxyborohydride (416 mg, 1.96 mmol, 3.0 eq) was added to above mixture and the resulting mixture was stirred at 40 °C for 16 h. After cooled to room temperature, the mixture was dissolve with EA (60 mL), washed with brine (30 mL x 4), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 90%) to afford tert-butyl 7-(2,6-dioxopiperidin-3-yl)-3',3'-difluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (220 mg, yeild 68.4%) as a grey solid. LC-MS (ESI): mass calcd. for $C_{24}H_{27}F_2N_3O_6$, 491.49; m/z found, 492.2 $[M+H]^+$.

Step I: afford 3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

[0409] To a solution of tert-butyl 7-(2,6-dioxopiperidin-3-yl)-3',3'-difluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (200 mg, 407 μmol, 1.0 eq) in DCM (5.00 mL) was added Trifluoroacetic acid (2.99 g, 2.00 mL, 26.3 mmol, 64.5 eq) and the reaction was stirred at 25 °C for 1 h. The mixture was concentrated and dried to afford 3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione trifluoroacetate (150 mg, yield 94%) as a grey solid. LC-MS (ESI): mass calcd. for $C_{19}H_{19}F_2N_3O_4$, 391.37; m/z found, 392.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (d, J = 4.4 Hz, 1H), 9.67 (s, 1H), 7.48 - 7.37 (m, 2H), 5.16 - 4.96 (m, 2H), 4.74 - 4.63 (m, 1H), 4.44 (t, J = 17.0 Hz, 1H), 4.27 (t, J = 16.6 Hz, 1H), 3.93 - 3.71 (m, 2H), 3.03 (t, J = 12.0 Hz, 1H), 2.97 - 2.83 (m, 1H), 2.60 (d, J = 17.2 Hz, 1H), 2.46 - 2.40 (m, 2H), 2.26 - 2.23 (m, 1H), 2.08 (d, J = 5.0 Hz, 1H), 2.00 - 1.98 (m, 1H).

Intermediate B11: (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



Step A: tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)-3,6-dihydropyridine-1(2H)-carboxylate

[0410] To a solution of 5-bromo-4-hydroxyisobenzofuran-1(3H)-one (10.0 g, 43.60 mmol, 1.0 eq) in THF (300 mL) were added tert-butyl- 4-(hydroxymethyl)-3,6-dihydropyridine-1(2H)-carboxylate (11.18 g, 52.4 mmol, 1.2 eq) and Triphenylphosphine (17.18 g, 65.4 mmol, 14.62 mL, 1.5 eq). The mixture was stirred under N_2 at 0 °C for 20 min. Then DIAD (13.24 g, 65.4 mmol, 12.74 mL, 1.5 eq) was dropwise added to above mixture and the mixture was stirred at room temperature overnight. After evaporation, the crude product was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 20%) to afford tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)-3,6-dihydropyridine-1(2H)-carboxylate (18.0 g, yield 97%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{19}H_{22}BrNO_5$, 424.29; m/z found, 369.9 $[M+H-56]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 5.89 (s, 1H), 5.66 (s, 2H), 4.66 (s, 2H), 3.88 (s, 2H), 3.48 (dd, J = 14.6, 9.0 Hz, 2H), 2.22 (s, 2H), 1.41 (s, 9H).

Step B: tert-butyl 6-oxo-2',3',6,8-tetrahydro-1'H,2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-pyridine]-1'-carboxylate

[0411] To a solution of tert-butyl 4-(((5-bromo-1-oxo-1,3-dihydroisobenzofuran-4-yl)oxy)methyl)-3,6-dihydropyridine-1(2H)-carboxylate (15.00 g, 23.70 mmol, 1.0 eq) in DMF (90.0 mL) were added sodium formate (1.77 g, 26.07 mmol, 1.1 eq), palladium diacetate (531 mg, 2.37 mmol, 0.1 eq), sodium acetate (4.86 g, 59.1 mmol, 2.5 eq), and TEA (4.32g, 26.07 mmol, 3.99 mL, 1.1 eq). The mixture was stirred under N_2 at 70 °C for 16 h. After cooled to room temperature, the mixture was filtered and the cake was washed with EA (300 mL). The filtrate was washed with brine (60 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 30%) to afford tert-butyl 6-oxo-2',3',6,8-tetrahydro-1'H,2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-pyridine]-1'-carboxylate (5.10 g, yield 62.7%) as a colorless oil. LC-MS (ESI): mass calcd. for $C_{19}H_{21}NO_5$, 343.38; m/z found, 344.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.41 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.03 - 6.98 (m, 1H), 5.38 (s, 2H), 4.88 - 4.82 (m, 1H), 4.60 (d, J = 9.2 Hz, 1H), 4.39 (d, J = 9.2 Hz, 1H), 3.81 - 3.75 (m, 1H), 3.47 - 3.41 (m, 1H), 2.02 - 1.98 (m, 1H), 1.84 - 1.78 (m, 1H), 1.47 (s, 9H).

Step C: tert-butyl 3'-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate

[0412] To a solution of tert-butyl 6-oxo-2',3',6,8-tetrahydro-1'H,2H-spiro[benzo[2,1-b:3,4-

c']difuran-3,4'-pyridine]-1'-carboxylate (5.10 g, 14.87 mmol, 1.0 eq) in THF (60.0 mL) was added BH_3-THF (1 *N*) (37.1 mL, 37.1 mmol, 2.5 eq) under N_2 at -78 °C. The reaction was allowed to slowly warm to 0 °C and stirred at 0 °C for 5 h. Water (10 mL) was added to above mixture, followed by Sodium perborate (6.07 g, 74.2 mmol, 5.0 eq). The resulting mixture was stirred overnight. The mixture was diluted with DCM (100 mL), washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 40%) to afforded tert-butyl 3'-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (2.93 g, yield 54%) as a white powder. LC-MS (ESI): mass calcd. for $C_{19}H_{23}NO_6$, 361.39; m/z found, 306.1 $[M+H-56]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 5.35 (d, J = 2.6 Hz, 2H), 5.31 (d, J = 4.6 Hz, 1H), 4.83 (d, J = 9.0 Hz, 1H), 4.53 (d, J = 9.0 Hz, 1H), 4.01 (s, 1H), 3.87 (s, 1H), 3.76 - 3.73 (m, 1H), 2.83 - 2.56 (m, 2H), 1.88 - 1.74 (m, 2H), 1.43 (s, 9H).

Step D: tert-butyl 3',6-dioxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate

[0413] To a solution of tert-butyl 3'-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (2.90 g, 8.10 mmol, 1.0 eq) in DCM (60.0 mL) was added Dess-Martin Periodinane (8.60 g, 20.35 mmol, 2.5 eq). The mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with aqueous sodium thiosulfate solution (60 mL) and extracted with DCM (90 mL x 3). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (60 mL x 2), brine (40 mL x 2), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford tert-butyl 3',6-dioxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (2.12 g, yield 72.6%) as a colorless oil. The crude product was directly used in next step without further purification. LC-MS (ESI): mass calcd. for $C_{19}H_{21}NO_6$, 359.38; m/z found, 360.1 $[M+H]^+$.

Step E: tert-butyl 3',6-dioxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate

[0414] To a solution of tert-butyl 3',6-dioxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (2.0 g, 5.57 mmol, 1.0 eq), triethylammoniumFluoride (5.38 g, 5.44 mL, 33.4 mmol, 6.0 eq), and N,N-Diethyl-S,S-difluoro-sulfiliminium tetrafluoroborate (XtalFluor-E) (5.73 g, 25.0 mmol, 4.5 eq) in DCM (100.0 mL) was added TEA (1.41 g, 1.94 mL, 13.9 mmol, 2.5 eq) at 0 °C and the mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (60 mL) and extracted with

DCM (100 mL x 3). The separated organic phase 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 silica gel chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 30%) to afford tert-butyl 3',3'-difluoro-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (1.0 g, yield 47%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{19}H_{21}F_2NO_5$, 381.38; m/z found, 382.1 $[M+H]^+$.

Step F: 1'-(tert-butoxycarbonyl)-3',3'-difluoro-7-(hydroxymethyl)-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid

[0415] To a solution of tert-butyl 3',3'-difluoro-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (280 mg, 734 μmol, 1.0 eq) in THF (9.00 mL), MeOH (9.00 mL), and H_2O (3.00 mL) was added NaOH (44 mg, 1.10 mmol, 1.5 eq). The mixture was stirred at 40 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with EA (20 mL), adjusted to pH = 4-5 with aqueous HCl solution (3 *N*), and extracted with EA (40 mL x 4). The organic layer was washed with brine (20 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to 1'-(tert-butoxycarbonyl)-3',3'-difluoro-7-(hydroxymethyl)-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (290 mg, yield 99%) as a colorless oil. The crude product was directly used in next step without purification. LC-MS (ESI): mass calcd. for $C_{19}H_{23}F_2NO_6$, 399.39; m/z found, 398.3 $[M-H]^-$.

Step G: tert-butyl 2,2-difluoro-8-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate

[0416] A solution of 1'-(tert-butoxycarbonyl)-3',3'-difluoro-7-(hydroxymethyl)-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylic acid (1.6 g, 4.01 mmol, 1.0 eq) and active Manganese dioxide (6.97 g, 80.1 mmol, 20.0 eq) in DCM (30.0 mL) was stirred at room temperature for 16 h. After filtration via a short column, the filtrate is collected and concentrated under reduced pressure to tert-butyl 2,2-difluoro-8-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (1.5 g, yield 96.6%) as a colorless oil. The crude product was directly used in next step without purification. LC-MS (ESI): mass calcd. for $C_{19}H_{21}F_2NO_6$, 397.37; m/z found, 398.1 $[M+H]^+$.

Step H: tert-butyl 7-((S)-1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-3',3'-difluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

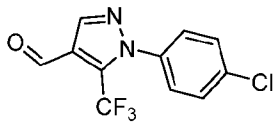
[0417] To a solution of tert-butyl 3',3'-difluoro-8-hydroxy-6-oxo-6,8-dihydro-2H-spiro[benzo[2,1-b:3,4-c']difuran-3,4'-piperidine]-1'-carboxylate (1.60 g, 4.03 mmol, 1.0 eq) and tert-butyl (*S*)-4,5-diamino-5-oxopentanoate hydrochloride (1.92 g, 8.05 mmol, 2.0 eq) in DMF (30.0 mL) was added Acetic acid (2.42 g, 2.32 mL, 40.3 mmol, 10.0 eq) and the

reaction mixture was stirred at 40 °C for 2 h. Sodium triacetoxyborohydride (2.56 g, 1.79 mL, 12.1 mmol, 3.0 eq) was added to above mixture and the resulting mixture was stirred at 40 °C for 16 h. After cooled to room temperature, the mixture was diluted with EA (100 mL), washed with brine (100 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 90%) to afford tert-butyl 7-((*S*)-1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-3',3'-difluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (1.80 g, yield 79%) as a white solid. LC-MS (ESI): mass calcd. for $C_{28}H_{37}F_2N_3O_7$, 565.61; m/z found, 566.4 $[M+H]^+$.

Step I: (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione benzenesulfonate

[0418] To a solution of tert-butyl 7-((*S*)-1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-3',3'-difluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (1.80 g, 3.18 mmol, 1.0 eq) in MeCN (30.0 mL) was added anhydrous benzenesulfonicacid (1.51 g, 9.55 mmol, 3.0 eq) and the reaction mixture was stirred under N_2 at 90 °C for 7 h. After cooled to room temperature, the mixture was concentrated and the residue was slurred with acetonitrile (30 mL) to afford (3*S*)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione benzenesulfonate (1.20 g, yield 68%) as a white solid. LC-MS (ESI): mass calcd. for $C_{19}H_{19}F_2N_3O_4$, 391.37; m/z found, 392.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (d, *J* = 4.6 Hz, 1H), 9.48 (s, 2H), 7.64 - 7.59 (m, 2H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.35 - 7.29 (m, 3H), 5.17 - 4.99 (m, 2H), 4.74 - 4.66 (m, 1H), 4.43 (t, *J* = 17.2 Hz, 1H), 4.27 (t, *J* = 17.2 Hz, 1H), 3.98 - 3.72 (m, 2H), 3.40 (d, *J* = 13.0 Hz, 1H), 3.06 - 2.88 (m, 2H), 2.60 - 2.58 (m, 1H), 2.46 - 2.38 (m, 2H), 2.27 - 2.22 (m, 1H), 2.01 - 1.98 (m, 1H).

Intermediate B12: 1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde



Step A: ethyl (Z)-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate

[0419] A mixture of ethyl 4,4,4-trifluoro-3-oxobutanoate (1.00 g, 5.43 mmol, 1.0 eq) and Acetic anhydride (1.66 g, 1.54 mL, 16.3 mmol, 3.0 eq) in Triethyl orthoformate (8.00 mL) was stirred at 130 °C for 4 h. The reaction mixture was concentrated under reduced pressure to give ethyl (Z)-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (1.20 g, yield 92%) as a

yellow oil. The crude product was directly used in next step without further purification. LC-MS: no ion signal was showed under routine conditions. LC-MS (ESI): mass calcd. for $C_9H_{11}F_3O_4$, 240.06; m/z found, 241.1 $[M+H]^+$.

Step B: ethyl 1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate

[0420] To a solution of ethyl (Z)-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (1.20 g, 5.00 mmol, 1.0 eq) in EtOH (30.0 mL) were added Triethylamine (607 mg, 836 μL, 6.00 mmol, 1.2 eq) and (4-chlorophenyl) hydrazine hydrochloride (1.07 g, 6.00 mmol, 1.2 eq) at room temperature. The mixture was heated to 100 °C for 5 h. After evaporation, the residue was diluted with ethyl acetate (50 mL), washed with brine (30 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (PE/EA = 50/1) to provide ethyl 1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (723 mg, yield 45%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{11}H_8D_2F_2N_2O$, 318.04; m/z found, 319.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.69 - 7.66 (m, 2H), 7.63 - 7.60 (m, 2H), 4.32 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H).

Step C: (1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)methanol

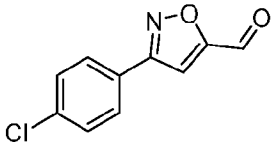
[0421] To a solution of ethyl 1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (350 mg, 1.10 mmol, 1.0 eq) in THF (10.0 mL) was added Aluminum lithium hydride (83.4 mg, 2.20 mmol, 20 eq) at 0 °C. The reaction mixture was stirring at 0 °C for 20 min. The reaction mixture was cautiously quenched by $Na_2SO_4 \cdot 10H_2O$ and stirred for 30 min. After filtration, the filtrate was diluted with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give (1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)methanol (300 mg, yield 98%) as a yellow oil. The crude product was directly used in next step without further purification. LC-MS (ESI): mass calcd. for $C_{11}H_8ClF_3N_2O$, 276.03; m/z found, 277.1 $[M+H]^+$.

Step D: 1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde

[0422] To a solution of (1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)methanol (300 mg, 1.08 mmol, 1.0 eq) in DMSO (10.0 mL) was added IBX (759 mg, 2.71 mmol, 2.5 eq) at room temperature. The reaction mixture was stirred at 25 °C for 30 min. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ solution (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over anhydrous sodium

sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chroatography on silica gel (PE/EA = 20/1) to provide 1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde (227 mg, yield 76%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{11}H_6ClF_3N_2O$, 274.01; m/z found, 275.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.44 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H).

Intermediate B13: 3-(4-chlorophenyl)isoxazole-5-carbaldehyde



Step A: (Z)-4-chlorobenzaldehyde oxime

[0423] A mixture of 4-chlorobenzaldehyde (6.00 g, 42.7 mmol, 1.0 eq), Hydroxylammoniumchloride (2.97 g, 42.7 mmol, 1.0 eq), and Cs_2CO_3 (2.26 g, 21.3 mmol, 0.5 eq) in MeOH (36.0 mL) and H_2O (18.00 mL) was stirred at 30 °C for 3 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (100 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0 to 20%) to afford (Z)-4-chlorobenzaldehyde oxime (5 g, yield 75%) as a white solid. LC-MS (ESI): mass calcd for: C_7H_6ClNO 155.01; m/z found, 156.0 $[M+H]^+$

Step B: (E)-4-chloro-N-hydroxybenzimidoyl chloride

[0424] To a solution of (Z)-4-chlorobenzaldehyde oxime (1.00 g, 6.43 mmol, 1 eq) in DMF (20 mL) was added NCS (171.6 mg, 1.286 mmol, 0.2 eq). Then NCS (686.4 mg, 5.144 mmol, 0.8 eq) was added in small portions and the resulting mixture was stirred at 30 °C for 24 h. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (50 mL x 3). The organic layer was washed with brine (50 mL x 4), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0 to 20%) to afford (E)-4-chloro-N-hydroxybenzimidoyl chloride (0.8 g, yield 66%) as a white solid. LC-MS (ESI): mass calcd for: $C_7H_5Cl_2NO$ 188.97; m/z found, 190.0 $[M+H]^+$.

Step C: (3-(4-chlorophenyl)isoxazol-5-yl)methanol

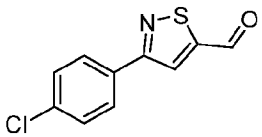
[0425] To a solution of (E)-4-chloro-N-hydroxybenzimidoyl chloride (0.6 g, 3.2 mmol, 1.0 eq) and Propargyl alcohol (0.19 g, 3.5 mmol, 1.1 eq) in *t*-BuOH (5.0 mL) and H_2O (5.0 mL) were added sodium ascorbate (63.0 mg, 0.32 mmol, 0.1 eq) and copper(II) sulfate pentahydrate

(24 mg, 95.0 μmol, 0.03 e). The reaction mixture was stirred for 30 min. Then $KHCO_3$ (961 mg, 9.6 mmol, 3.0 eq) was added to above mixture and the resulting mixture was stirred at 30 °C for 1.5 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (30 mL x 3). The organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0 to 35%) to afford (3-(4-chlorophenyl)isoxazol-5-yl)methanol (0.38 g, yield 57%) as a white solid. LC-MS (ESI): mass calcd for: $C_{10}H_8ClNO_2$ 209.02; m/z found, 210.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 8.6 Hz, 1H), 6.96 (s, 1H), 5.73 (t, J = 6.0 Hz, 1H), 4.61 (d, J = 6.0 Hz, 2H).

Step D: 3-(4-chlorophenyl)isoxazole-5-carbaldehyde

[0426] To a solution of (3-(4-chlorophenyl)isoxazol-5-yl)methanol (120 mg, 572 μmol, 1.0 eq) in DCM (5.0 mL) was added Dess-Martin Periodinane (267 mg, 630 μmol, 1.1 eq). The mixture was stirred at room temperature for 2 h. The reaction was diluted with EA (60 mL), washed with saturated aqueous NaS_2O_3 solution (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (EA/PE = 1/10) to give 3-(4-chlorophenyl)isoxazole-5-carbaldehyde (100 mg, yield 84%) as a yellow solid. LC-MS (ESI): mass calcd for: $C_{10}H_6ClNO_2$ 207.01; m/z found, No MS signal found.

Intermediate B14: 3-(4-chlorophenyl)isothiazole-5-carbaldehyde



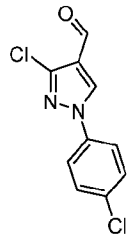
Step A: 3-(4-chlorophenyl)isothiazole

[0427] A mixture of 3-bromoisothiazole (100 mg, 610 μmol, 1.0 eq), (4-chlorophenyl) boronic acid (143 mg, 915 μmol, 1.5 eq), tetrakis(triphenylphosphine)palladium(o) (70.5 mg, 61.0 μmol, 0.1 eq), and Potassium carbonate (169 mg, 1.2 mmol, 2.0 eq) in 1,4-Dioxane (6.0 mL) and H_2O (1.0 mL) was stirred under N_2 at 80 °C for 4 h. After cooled to room temperature, the mixture was diluted with DCM (50 mL) and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by Prep-TLC (EA/PE = 1/10) to give 3-(4-chlorophenyl)isothiazole (82.0 mg, yield 68%) as a yellow oil. LC-MS (ESI): mass calcd. for C_9H_6ClNS, 195.0; m/z found, 196.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.18 (d, J = 0.6 Hz, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 0.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H).

Step B: 3-(4-chlorophenyl)isothiazole-5-carbaldehyde

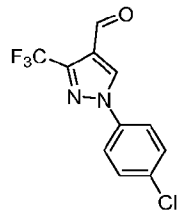
[0428] To a mixture of 3-(4-chlorophenyl)isothiazole (50.0 mg, 256 μmol, 1.0 eq) in anhydrous THF (5.0 mL) was added n-butyllithium (2.5 *M* in n-hexane) (0.16 mL, 384 μmol, 1.5 eq) under N_2 at -78 °C and the mixture was stirred at this temperature for 30 min. Then anhydrous DMF (93.4 mg, 1.3 mmol, 5.0 eq) was added to above mixture and the resulting mixture was stirred under N_2 at -78 °C for 30 min. The mixture was quenched by the addition of saturated aqueous NH_4Cl solution (20 mL), stirred for 15 min, and extracted with EA (20 mL x 4). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (EA/PE = 1/10) to give 3-(4-chlorophenyl)isothiazole-5-carbaldehyde (28.0 mg, yield 49%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{10}H_6ClNOS$, 223.0; m/z found, 224.1 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.72 (s, 1H), 8.11 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H).

Intermediate B15: 3-chloro-1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde



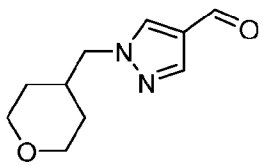
[0429] $POCl_3$ (5.51 g, 3.35 mL, 36.0 mmol, 7.0 eq) was added dropwise to DMF (10.0 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 5 min. 1-(4-chlorophenyl)-1,2-dihydro-3H-pyrazol-3-one (1.00 g, 5.14 mmol, 1.0 eq) was added to above mixture and the resulting reaction mixture was heated to 105 °C and stirred for 16 h. After cooled to room temperature, the mixture was poured into crushed ice and brown solid was precipitated. The solid was collected by filtration, washed with water (30 mL). The solid cake was dissolved in DCM (150 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 10/1) to give 3-chloro-1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde (40.0 mg, yield 3%) as a yellow solid. LC-MS (ESI): mass calced for: $C_{10}H_8N_2O$ 172.19; m/z no mass signal. ^1H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 9.33 (s, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H).

Intermediate B16: 1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde



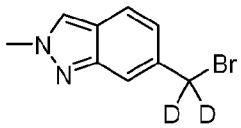
[0430] A mixture of 3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde (50.0 mg, 305 μmol, 1.0 eq), Copper diacetate (111 mg, 609 μmol, 2.0 eq), (4-chlorophenyl)boronic acid (71.5 mg, 457 μmol, 1.5 eq), 2,2'-Bipyridine (95.2 mg, 609 μmol, 2.0 eq), and Sodium carbonate (161 mg, 1.5 mmol, 5.0 eq) in DCE (6.0 mL) was stirred under O_2 at 70 °C for 5 h. After cooled to room temperature, the mixture was filtered and the filtrate was quenched with water (20 m), and extracted with DCM (20 mL x 3). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by Prep-TLC (EA/PE = 3/1) to give 1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde (34.0 mg, yield 41%) as a white solid. LC-MS (ESI): mass calcd. for $C_{11}H_6ClF_3N_2O$, 274.0; m/z no signal. ^1H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.51 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H).

Intermediate B17: 1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazole-4-carbaldehyde



[0431] To a solution of 1H-pyrazole-4-carbaldehyde (1.95 g, 20.3 mmol, 1.0 eq) and Cs_2CO_3 (13.2 g, 40.5 mmol, 2.0 eq) in DMF (5.00 mL) was added 4-(bromomethyl)tetrahydro-2H-pyran (5.44 g, 30.4 mmol, 1.5 eq). The reaction mixture was stirred at 80 °C for 16 h. After cooled to room temperature, the mixture was diluted with EA (100 mL), washed with brine (50 mL x 4), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (PE/EA = 1/1) to obtain 1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazole-4-carbaldehyde (2 g, yield 50%) as a yellow solid. LC-MS (ESI): mass calced for: $C_{10}H_{14}N_2O_2$ 194.11; m/z found, 195.1 $[M+H]^+$.

Intermediate B18: 6-(bromomethyl-d_2)-2-methyl-2H-indazole



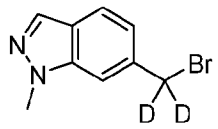
Step A: (2-methyl-2H-indazol-6-yl)methan-d_2-ol

[0432] To a solution of methyl 2-methyl-2H-indazole-6-carboxylate (400 mg, 2.10 mmol, 1.0 eq) in THF (8.00 mL) was added $LiAlD_4$ (88.3 mg, 2.10 mmol, 1.0 eq) at 0 °C in portions and the reaction mixture was stirred at 0 °C for 0.5 h. The reaction mixture was diluted with EtOAc (30 mL), cautiously quenched with sodium sulfate decahydrate and stirred for 0.5 h. After filtration, the filtrate was concentrated under reduced pressure to afford (2-methyl-2H-indazol-6-yl)methan-d_2-ol (340 mg, yield 98%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_9H_8D_2N_2O$, 164.20; m/z found, 165.1 $[M+H]^+$.

Step B: 6-(bromomethyl-d_2)-2-methyl-2H-indazole

[0433] To a solution of (2-methyl-2H-indazol-6-yl)methan-d_2-ol (340 mg, 2.07 mmol, 1.0 eq) in DCM (5.0 mL) was added Triphenylphosphine (815 mg, 3.11 mmol, 1.5 eq) and the mixture was stirred under the atmosphere at 50 °C for 5 min. Then a solution of CBr4 (1.03 g, 3.11 mmol, 1.5 eq) in DCM (5.0 mL) was added to above mixture and the reaction mixture was stirred at 50 °C for 2 h. After evaporation, the residue was purified by flash column chromatography on silica gel (PE/EA = 2/1) to obtain 6-(bromomethyl-d_2)-2-methyl-2H-indazole (100 mg, yield 21%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_9H_7D_2BrN_2$, 226.01; m/z found, 227.0 $[M+H]^+$.

Intermediate B19: 6-(bromomethyl-d_2)-1-methyl-1H-indazole



Step A: methyl 1-methyl-1H-indazole-6-carboxylate and methyl 2-methyl-2H-indazole-6-carboxylate

[0434] To a solution of methyl 1H-indazole-6-carboxylate (2.00 g, 11.4 mmol, 1.0 eq) and iodomethane (4.83 g, 34.1 mmol, 3.0 eq) in DMF (20 mL) was added cesium carbonate (7.40 g, 22.7 mmol, 2.0 eq) and the reaction mixture was stirred at room temperature for 2 h. After filtered, The filtration was diluted with EtOAc (100 mL) and washed with brine (30 mL x 5). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/EA = 1/1) to obtain methyl 1-methyl-1H-indazole-6-carboxylate (1.35 g, yield 62%) as a

yellow solid and methyl 2-methyl-2H-indazole-6-carboxylate (800 mg, yield 37%) as a yellow oil.

[0435] Methyl 1-methyl-1H-indazole-6-carboxylate: LC-MS (ESI): mass calcd. for $C_{10}H_{10}N_2O_2$, 190.20; m/z found, 191.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 3H), 8.17 (s, 1H), 7.92 - 7.84 (m, 1H), 7.70 (dd, J = 8.4, 1.2 Hz, 1H), 4.14 (s, 3H), 3.91 (s, 3H).

[0436] Methyl 2-methyl-2H-indazole-6-carboxylate: LC-MS (ESI): mass calcd. for $C_{10}H_{10}N_2O_2$, 190.20; m/z found, 191.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.28 (s, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.56 (dd, J = 8.8, 1.2 Hz, 1H), 4.23 (s, 3H), 3.88 (s, 3H).

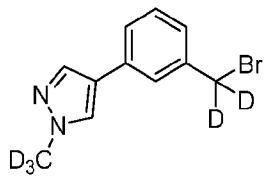
Step B: (1-methyl-1H-indazol-6-yl)methan-d_2-ol

[0437] To a solution of methyl 1-methyl-1H-indazole-6-carboxylate (700 mg, 3.68 mmol, 1.0 eq) in THF (20 mL) was added $LiAlD_4$ (155 mg, 3.68 mmol, 1.0 eq) in portions at 0 °C and the reaction mixture was stirred at 0 °C for 0.5 h. The reaction was diluted with EtOAc (50 mL), quenched with sodium sulfate decahydrate, and stirred for 0.5 h. After filtration, the filtrate was concentrated under reduced pressure to afford (1-methyl-1H-indazol-6-yl)methan-d_2-ol (600 mg, yield 99%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_9H_8D_2N_2O$, 164.20; m/z found, 165.1 $[M+H]^+$.

Step C: 6-(bromomethyl-d_2)-1-methyl-1H-indazole

[0438] To a solution of (1-methyl-1H-indazol-6-yl)methan-d_2-ol (500 mg, 3.05 mmol, 1.0 eq) in DCM (5.0 mL) was added Triphenylphosphine (1.20 g, 4.57 mmol, 1.5 eq) and the mixed solution was stirred under the atmosphere at 50 °C for 5 min. Then a solution of CBr_4 (1.51 g, 4.57 mmol, 1.5 eq) in DCM (5.0 mL) was added dropwise to above mixture and the resulting reaction mixture was stirred at 50 °C for 2 h. After evaporation, the residue was purified by flash column chromatography on silica gel (PE/EA = 2/1) to obtain 6-(bromomethyl-d_2)-1-methyl-1H-indazole (300 mg yield 43%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_9H_7D_2BrN_2$, 226.01; m/z found, 227.0 $[M+H]^+$.

Intermediate B20: 4-(3-(bromomethyl-d2)phenyl)-1-(methyl-d3)-1H-pyrazole



Step A: 4-bromo-1-(methyl-d_3)-1H-pyrazole

[0439] To a solution of 4-bromo-1H-pyrazole (1.00 g, 6.80 mmol, 1.0 eq) in DMF (5.00 mL) were added Cs_2CO_3 (4.43 g, 13.6 mmol, 2.0 eq) and iodomethane-d_3 (635 μL, 10.2 mmol, 1.5

eq). The reaction mixture was stirred at room temperature for 16 h. After filtration, the mixture was diluted with EA (30 mL), washed with brine (20 mL x 4), dried over anhydrous sodium sulfate, filtered and concentrate under reduced pressure to give 4-bromo-1-(methyl-d_3)-1H-pyrazole (1.10 g, yield 98%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_4H_2D_3BrN_2$, 162.99; m/z found, 164.1 $[M+H]^+$.

Step B: methyl 3-(1-(methyl-d_3)-1H-pyrazol-4-yl)benzoate

[0440] To a solution of 4-bromo-1-(methyl-d_3)-1H-pyrazole (500 mg, 3.05 mmol, 1.0 eq), (3-(methoxycarbonyl) phenyl)boronic acid (658 mg, 3.66 mmol, 1.2 eq), and potassium carbonate (1.26 g, 9.15 mmol, 3.0 eq) in 1,4-Dioxane (10.0 mL) and water (0.10 mL) was added $Pd(dppf)Cl_2$ (249 mg, 305 μmol, 0.1 eq). The reaction mixture was stirred under N_2 at 100 °C for 2 h. After cooled to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EA/PE = 1/1) to give methyl 3-(1-(methyl-d_3)-1H-pyrazol-4-yl) benzoate (400 mg, yield 60%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{12}H_9D_3N_2O_2$, 219.11; m/z found, 220.2 $[M+H]^+$.

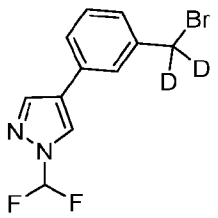
Step C: (3-(1-(methyl-d_3)-1H-pyrazol-4-yl)phenyl)methan-d_2-ol

[0441] To a solution of methyl 3-(1-(methyl-d_3)-1H-pyrazol-4-yl) benzoate (400 mg, 1.82 mmol, 1.0 eq) in THF (10.0 mL) was added $LiAlD_4$ (153 mg, 3.65 mmol, 2.0 eq) in portions at 0 °C. The reaction mixture was stirred at 0 °C for 40 min. The mixture was cautiously quenched with sodium sulfate decahydrate (500 mg) and filtered. The filtrate was concentrated under reduced pressure to give (3-(1-(methyl-d_3)-1H-pyrazol-4-yl)phenyl)methan-d_2-ol (300 mg, yield 85%) as a white solid. LC-MS (ESI): mass calcd. for $C_{11}H_7D_5N_2O$, 193.12; m/z found, 194.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.54 (s, 1H), 7.41 (s, 1H), 7.34 - 7.25 (m, 2H), 7.14 (d, J = 7.4 Hz, 1H).

Step D: 4-(3-(bromomethyl-d_2)phenyl)-1-(methyl-d_3)-1H-pyrazole

[0442] To a solution of (3-(1-(methyl-d_3)-1H-pyrazol-4-yl) phenyl)methan-d_2-ol (300 mg, 1.55 mmol, 1.0 eq) and triphenylphosphine (611 mg, 2.33 mmol, 1.5 eq) in DCM (5.00 mL) was added CBr_4 (772 mg, 2.33 mmol, 1.5 eq) under N_2. The reaction mixture was stirred at 50 °C for 2 h. After evaporation, the residue was purified by flash column chromatography on silica gel (EA/PE = 1/1) to give 4-(3-(bromomethyl-d_2)phenyl)-1-(methyl-d_3)-1H-pyrazole (350 mg, yield 88%) as a white solid. LC-MS (ESI): mass calcd. for $C_{11}H_6D_5BrN_2$, 255.04; m/z found, 256.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.87 (s, 1H), 7.65 (s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H).

Intermediate B21: 4-(3-(bromomethyl-d_2) phenyl)-1-(difluoromethyl)-1H-pyrazole



Step A: methyl 3-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzoate

[0443] To a solution of 4-bromo-1-(difluoromethyl)-1H-pyrazole (500 mg, 2.54 mmol, 1.0 eq), (3-(methoxycarbonyl) phenyl) boronic acid (548 mg, 3.05 mmol, 1.2 eq), and Cesium carbonate (2.48 g, 7.61 mmol, 3.0 eq) in 1,4-Dioxane (20.0 mL) and Water (5.00 mL) was added 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (186 mg, 254 μmol, 1.0 eq). The reaction mixture was stirred under nitrogen at 90 °C for 2 h. After cooled to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (PE/EA = 20/1) to provide methyl 3-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzoate (580 mg, yield 90%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{12}H_{10}F_2N_2O_2$, 252.07; m/z found, 253.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.37 (s, 1H), 8.24 (t, J = 1.6 Hz, 1H), 8.02 - 7.97 (m, 1H), 7.89 - 7.87 (m, 1H), 7.86 (t, J = 67.6 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 3.89 (s, 3H).

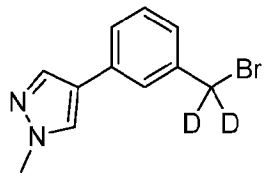
Step B: (3-(1-(difluoromethyl)-1H-pyrazol-4-yl) phenyl)methan-d_2-ol

[0444] To a solution of methyl 3-(1-(difluoromethyl)-1H-pyrazol-4-yl)benzoate (200 mg, 793 μmol, 1.0 eq) in dry THF (10.0 mL) was added $LiAlD_4$ (66.6 mg, 1.59 mmol, 2.0 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. The reaction mixture was cautiously quenched with $Na_2SO_4 \cdot 10H_2O$ and stirred for 30 min. After Filtration, the filtrate was diluted with water and extracted with ethyl acetate (25 mL x 3). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (PE/EA = 4/1) to provide (3-(1-(difluoromethyl)-1H-pyrazol-4-yl)phenyl)methan-d_2-ol (158 mg, yield 88%) as a yellow oil. LC-MS (ESI): mass calcd. for C11H8D2F2N2O, 226.09; m/z found, 227.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.29 (s, 1H), 7.93 (t, J = 67.6 Hz, 1H), 7.69 - 7.55 (m, 2H), 7.41 (d, J = 7.6 Hz, 1H), 7.32 - 7.23 (m, 1H), 5.22 (s, 1H).

Step C: 4-(3-(bromomethyl-d_2) phenyl)-1-(difluoromethyl)-1H-pyrazole

[0445] To a solution of (3-(1-(difluoromethyl)-1H-pyrazol-4-yl)phenyl)methan-d_2-ol (145 mg, 641 μmol, 1.0 eq) in DCM (10.0 mL) were added Triphenylphosphine (252 mg, 961 μmol, 1.5 eq) and carbon tetrabromide (319 mg, 961 μmol, 1.5 eq). The reaction mixture was stirred at 50 °C for 1 h. After cooled to room temperature, the reaction mixture was diluted with DCM (20 mL), washed with saturated aqueous sodium bicarbonate (20 mL), water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EA = 10/1) to provide 4-(3-(bromomethyl-d_2)phenyl)-1-(difluoromethyl)-1H-pyrazole (172 mg, yield 93%) as a white solid. LC-MS (ESI): mass calcd. for $C_{11}H_7D_2BrF_2N_2$, 288.00; m/z found, 289.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.29 (s, 1H), 7.85 (t, J = 59.2 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.67 - 7.63 (m, 1H), 7.43 - 7.35 (m, 2H).

Intermediate B22: 4-(3-(bromomethyl-d2)phenyl)-1-methyl-1H-pyrazole



Step A: methyl 3-(1-methyl-1H-pyrazol-4-yl)benzoate

[0446] To a solution of 4-bromo-1-methyl-1H-pyrazole (6.00 g, 37.3 mmol, 1.0 eq), (3-(methoxycarbonyl)phenyl) boronic acid (8.05 g, 44.7 mmol, 1.2 eq), and potassium carbonate (15.5 g, 112 mmol, 3.0 eq) in 1,4-Dioxane (80.0 mL) and Water (8.00 mL) was added Pd(dppf)Cl_2 (1.52 g, 1.86 mmol, 0.05 eq). The reaction mixture was stirred under N_2 at 100 °C for 3 h. After cooled to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to give methyl 3-(1-methyl-1H-pyrazol-4-yl) benzoate (6.50 g, yield 80%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{12}H_{12}N_2O_2$, 216.09; m/z found, 217.1 $[M+H]^+$.

Step B: (3-(1-methyl-1H-pyrazol-4-yl)phenyl)methan-d_2-ol

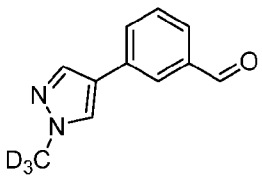
[0447] To a solution of methyl 3-(1-methyl-1H-pyrazol-4-yl) benzoate (7.50 g, 34.7 mmol, 1.0 eq) in dry THF (50.0 mL) was added $LiAlD_4$ (2.18 g, 52.0 mmol, 1.5 eq) in portions at 0 °C. The reaction mixture was stirred at 0 °C for 40 min. Then sodium sulfate decahydrate (5 g) was cautiously added to above mixture and filtered. The filtrate was concentrated under reduced pressure to give (3-(1-methyl-1H-pyrazol-4-yl)phenyl)methan-d_2-ol (5.30 g, yield 80%) as a white solid. LC-MS (ESI): mass calcd. for $C_{11}H_{10}D_2N_2O$, 190.11; m/z found, 191.1 $[M+H]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.55 (s, 1H), 7.41 (s, 1H), 7.34 - 7.26 (m, 2H), 7.15 (d, J = 7.4 Hz, 1H), 3.87 (s, 3H).

Step C: 4-(3-(bromomethyl-d_2)phenyl)-1-methyl-1H-pyrazole

[0448] To a solution of (3-(1-methyl-1H-pyrazol-4-yl)phenyl)methan-d_2-ol (500 mg, 2.63 mmol, 1.0 eq) in DCM (10.0 mL) was added triphenylphosphine (1.03 g, 3.94 mmol, 1.5 eq) at room temperature. Then A solution of perbromo methane (1.31 g, 3.94 mmol, 1.5 eq) in DCM (3 mL) was added to above mixture under N_2 and the resulting mixture was stirred under N_2 at 50 °C for 2 h. After evaporation, the residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, 17% v/v) to give 4-(3-(bromomethyl-d2)phenyl)-1-methyl-1H-pyrazole (490 mg, yield 74%) as a white solid. LC-MS (ESI): mass calcd. for $C_{11}H_9D_2BrN_2$, 252.02; m/z found, 253.2 $[M+H]^+$.

Intermediate B23: 3-(1-(methyl-d_3)-1H-pyrazol-4-yl)benzaldehyde



Step A: 4-bromo-1-(methyl-d_3)-1H-pyrazole

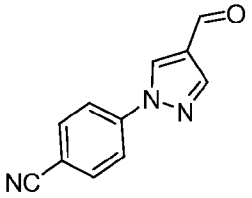
[0449] To a solution of 4-bromo-1H-pyrazole (3.00 g, 20.4 mmol, 1.0 eq) in DMF (60.0 mL) was added Cesium carbonate (13.3 g, 40.8 mmol, 2.0 eq) and the reaction mixture was stirred at room temperature for 1 h. Then CD_3I (5.92 g, 2.54 mL, 40.8 mmol, 2.0 eq) was dropwise added to above mixture and the resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EA (200 mL) and filtered. The filtrate was washed with brine (100 mL x 5), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 4-bromo-1-(methyl-d_3)-1H-pyrazole (2.40 g, yield 72%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_4H_2D_3BrN_2$, 162.98; m/z found, 164.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.44 (s, 1H).

Step B: 3-(1-(methyl-d_3)-1H-pyrazol-4-yl)benzaldehyde

[0450] To a solution of (3-formylphenyl)boronic acid (2.00 g, 13.3 mmol, 1.0 eq), 4-bromo-1-(methyl-d_3)-1H-pyrazole (2.84 g, 17.3 mmol, 1.3 eq), and Cesium carbonate (13.0 g, 40.0 mmol, 3.0 eq) in 1,4-Dioxane (70.0 mL) and water (20.0 mL) was added 1,1'-bis(diphenyl phosphino)ferrocene-palladium(II) dichloride (976 mg, 1.33 mmol, 0.1 eq). The reaction mixture was stirred under nitrogen at 90 °C for 1 h. After cooled to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The

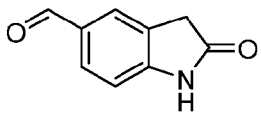
crude product was purified by flash column chromatography on silica gel (PE/EA = 2/1) to provide 3-(1-(methyl-d_3)-1H-pyrazol-4-yl)benzaldehyde (1.85 g, yield 73%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{11}H_7D_3N_2O$, 189.10; m/z found, 190.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.27 (s, 1H), 8.09 (s, 1H), 7.97 (s, 1H), 7.93 - 7.88 (m, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H).

Intermediate B24: 4-(4-formyl-1H-pyrazol-1-yl)benzonitrile



[0451] To a solution of 1H-pyrazole-4-carbaldehyde (5.0 g, 52.0 mmol, 1.0 eq) in DMF (50 mL) was added NaH (60% suspend in oil) (1.5 g, 62.4 mmol, 1.2 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. 4-fluorobenzonitrile (6.9 g, 57.2 mmol, 1.1 eq) was added to above mixture and the reaction mixture was stirred at 25 °C for 16 h. The mixture was quenched with H_2O (100 mL) and extracted with EtOAc (50 mL x 3). The organic layer was washed with brine (100 mL x 4), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE/EA = 2/1) to give 4-(4-formyl-1H-pyrazol-1-yl)benzonitrile (3.0 g, yield 29%) as a white solid. LC-MS (ESI): mass calcd. for $C_{11}H_7N_3O$, 197.06; m/z found, no Mass $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 9.41 (s, 1H), 8.37 (s, 1H), 8.15 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H).

Intermediate B25: 2-oxoindoline-5-carbaldehyde



Step A: 5-vinylindolin-2-one

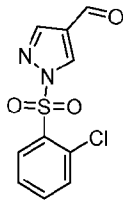
[0452] To a mixture of 5-bromoindolin-2-one (1.0 g, 4.72 mmol, 1.0 eq) and Potassium ethenyltrifluoroborate (948 mg, 7.07 mmol, 1.5 eq) in 1,4-Dioxane (20.0 mL) and H_2O (2.00 mL) were added $Pd(PPh_3)_4$ (545 mg, 472 μmol, 0.1 eq) and Na_2CO_3 (1.50 g, 14.1 mmol, 3.0 eq). The reaction mixture was stirred under N_2 at 100 °C for 4 h. After cooled to room temperature, the mixture was filtered and the filtrate was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4,

filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel（PE/EtOAc = 1/1) to give 5-vinylindolin-2-one (500 mg, yield 66%) as a brown solid. LC-MS (ESI): mass calcd. for $C_{10}H_9NO$, 159.07; m/z found, 160.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 7.36 (s, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.66 (dd, J = 17.6, 10.8 Hz, 1H), 5.66 (d, J = 17.6 Hz, 1H), 5.09 (d, J = 10.8 Hz, 1H), 3.47 (s, 2H).

Step B: 2-oxoindoline-5-carbaldehyde

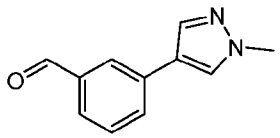
[0453] Ozone was bubbled into a solution of 5-vinylindolin-2-one (200 mg, 1.26 mmol, 1.0 eq) in DCM (10.0 mL) at -78 °C for 1 h. On completion, excess Ozone was purged from the reaction mixture with nitrogen. Then dimethylsulfide (5 mL) was added to above mixture and the reaction mixture was stirred for 30 min. After evaporation, the residue was purified by flash column chromatography on silica gel (PE/EA = 1/1) to give 2-oxoindoline-5-carbaldehyde (180 mg, yield 89%) as a light yellow solid. LC-MS (ESI): mass calcd. for $C_9H_7NO_2$, 161.05; m/z found, 162.2 $[M+H]^+$.

Intermediate B26: 1-((2-chlorophenyl)sulfonyl)-1H-pyrazole-4-carbaldehyde



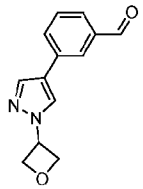
[0454] To a solution of 1H-pyrazole-4-carbaldehyde (500 mg, 5.20 mmol, 1.0 eq) and triethylamine (796 μL, 5.72 mmol, 1.1 eq) in DCM (5.00 mL) was added 2-chlorobenzenesulfonyl chloride (1.10 g, 5.20 mmol, 1.0 eq) in portions. The reaction mixture was stirred at room temperature for 2 h. After filtration, the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (EA/PE = 1/10) to give 1-((2-chlorophenyl)sulfonyl)-1H-pyrazole-4-carbaldehyde (780 mg, yield 55%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{10}H_7ClN_2O_3S$, 269.99; m/z found, 271.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 9.42 (s, 1H), 8.36 - 8.28 (m, 2H), 7.91 - 7.82 (m, 1H), 7.81 - 7.68 (m, 2H).

Intermediate B27: 3-(1-methyl-1H-pyrazol-4-yl) benzaldehyde



[0455] To a solution of 3-bromobenzaldehyde (5.00 g, 27.0 mmol, 1.0 eq), (1-methyl-1H-pyrazol-4-yl)boronic acid (4.08 g, 32.4 mmol, 1.2 eq), and Cesium carbonate (26.4 g, 81.1 mmol, 3.0 eq) in 1,4-Dioxane (100 mL) and Water (30.0 mL) was added 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (1.98 g, 2.70 mmol, 0.1 eq). The reaction mixture was stirred under nitrogen at 95 °C for 2 h. After cooled to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (PE/EA = 1/1) to provide 3-(1-methyl-1H-pyrazol-4-yl)benzaldehyde (4.00 g, yield 79%) as a yellow oil. LC-MS (ESI): mass calcd. for $C_{11}H_{10}N_2O$, 186.08; m/z found, 187. $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.27 (s, 1H), 8.08 (s, 1H), 7.97 (s, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 3.89 (s, 3H).

Intermediate B28: 3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzaldehyde



Step A: 4-bromo-1-(oxetan-3-yl)-1H-pyrazole

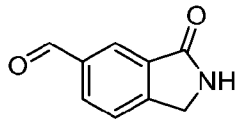
[0456] A mixture of 4-bromo-1H-pyrazole (500 mg, 3.40 mmol, 1.0 eq), 3-iodooxetane (626 mg, 3.40 mmol, 1.0 eq), and Cesium carbonate (1.11 g, 3.40 mmol, 1.0 eq) in DMF (5.00 mL) was stirred at 100 °C for 18 h. After cooled to room temperature, the reaction mixture was quenched with water (30 mL) and extracted with DCM (40 mL x 3). The organic layer was washed with brine (30 mL x 4), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 4-bromo-1-(oxetan-3-yl)-1H-pyrazole (620 mg, yield 89%) as a yellow solid. LC-MS (ESI): mass calcd for: $C_6H_7BrN_2O$ 203.04; m/z found, No mass signal. ^1H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.69 (s, 1H), 5.59 - 5.51 (m, 1H), 4.91 - 4.82 (m, 4H).

Step B: 3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzaldehyde

[0457] A mixture of 4-bromo-1-(oxetan-3-yl)-1H-pyrazole (620 mg, 3.05 mmol, 1.0 eq), (3-formylphenyl)boronic acid (916 mg, 6.11 mmol, 2.0 eq), Cs_2CO_3 (1.99 g, 6.11 mmol, 2.0 eq), and 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (223 mg, 305 μmol,

0.1 eq) in 1,4-Dioxane (10.0 mL) and H_2O (1.00 mL) was stirred under N_2 atmosphere at 95 °C for 18 h. After cooled to room temperature, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (30 mL x 3). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (methanol in dichloromethane, from 0 to 5%) to afford 3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzaldehyde (500 mg, yield 68%) as a yellow solid. LC-MS (ESI): mass calced for: $C_{13}H_{12}N_2O_2$ 228.25; m/z found, 229.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.53 (s, 1H), 8.15 (s, 2H), 7.96 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 5.65 - 5.57 (m, 1H), 4.98 - 4.91 (m, 4H).

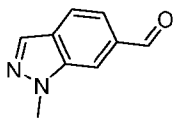
Intermediate B29: 3-oxoisoindoline-5-carbaldehyde



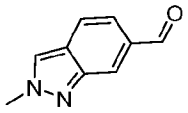
[0458] The intermediate was prepared according to the procedure described in Journal of Pharmaceutical Science & Technology (2010), 2(12), 380-390 as a white solid. The analytical data is consistent with the report in the literature.

Intermediate B30a: 1-methyl-1H-indazole-6-carbaldehyde

Intermediate B30b :2-methyl-2H-indazole-6-carbaldehyde



INT B30a



INT B30b

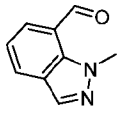
[0459] To a solution of 1H-indazole-6-carbaldehyde (1.00 g, 6.84 mmol, 1.0 eq) and K_2CO_3 (1.89 g, 13.7 mmol, 2.0 eq) in DMF (10.0 mL) was added MeI (1.46 g, 10.3 mmol, 1.5 eq) and the mixture was stirred at 30 °C for 2 h. The reaction mixture was diluted with H_2O (30 mL) and washed with brine and extracted with EA (30 ml x 3). The organic phase was washed with brine (30 mL x 4), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to v/v) to give 1-methyl-1H-indazole-6-carbaldehyde (600 mg, yield 54%) as a yellow solid and 2-methyl-2H-indazole-6-carbaldehyde (360 mg, yield 32%).

[0460] INT B30a, 1-methyl-1H-indazole-6-carbaldehyde: LC-MS (ESI) mass calced for: $C_9H_8N_2O$, 160.06; m/z found, 161.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.33 (s, 1H), 8.21 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 4.16 (s, 3H).

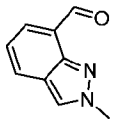
[0461] INT B30b: 2-methyl-2H-indazole-6-carbaldehyde: LC-MS (ESI) mass calced for: $C_9H_8N_2O$, 160.06; m/z found, 161.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.49 (s, 1H), 8.32 (s, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 4.25 (s, 3H).

Intermediate B31a:1-methyl-1H-indazole-7-carbaldehyde

Intermediate B31b: 2-methyl-2H-indazole-7-carbaldehyde



INT B31a



INT B31b

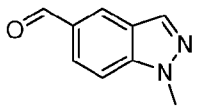
[0462] To a solution of 1H-indazole-7-carbaldehyde (300 mg, 2.05 mmol, 1.0 eq) in DMF (6.00 mL) were added potassium carbonate (851 mg, 6.16 mmol, 3.0 eq) and iodomethane (583 mg, 4.11 mmol, 2.0 eq). The reaction was stirred under N_2 atmosphere at room temperature for 2 h. After filtration, the filtrate was diluted with H_2O (15 mL) and extracted with EA (15 mL x 3). The organic layer was washed with brine (15 mL x 4), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC with YMC-Actus Triart C18 (5 um, 20 x 250 mm), and mobile phase of 5-95% ACN in water (0.1% TFA) over 20 min and then hold at 100% ACN for 2 min, at a flow rate of 25 mL/min to to obtained 2-methyl-2H-indazole-7-carbaldehyde (60 mg, yield 11%) as a yellow solid and 1-methyl-1H-indazole-7-carbaldehyde (110 mg, yield 20.1%) as a white solid.

[0463] INT B31a, 2-methyl-2H-indazole-7-carbaldehyde: LC-MS (ESI): mass calced for: $C_9H_8N_2O$ 160.18; m/z found, 161.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.59 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 7.0 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 4.25 (s, 3H).

[0464] INT B31b: 1-methyl-1H-indazole-7-carbaldehyde: LC-MS (ESI): mass calced for: $C_9H_8N_2O$ 160.18; m/z found, 161.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.25 (s, 1H), 8.15 (dd, J = 8.0, 1.0 Hz, 1H), 8.04 (dd, J = 7.2, 1.0 Hz, 1H), 7.43 - 7.25 (m, 1H), 4.36 (s, 3H).

Intermediate B32a: 1-methyl-1H-indazole-5-carbaldehyde

Intermediate B32b: 2-methyl-2H-indazole-5-carbaldehyde



INT B32a

INT B32b

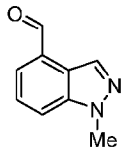
[0465] To a solution of 1H-indazole-5-carbaldehyde (1.0 g, 6.8 mmol, 1.0 eq) in DMF (20.0 mL) was added Potassium carbonate (2.8 g, 20.5 mmol, 3.0 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. Then methyl iodide (1.9 g, 13.7 mmol, 2.0 eq) was dropwise added to above mixture at 0 °C. The mixture was stirred at 25 °C for 50 min. The reaction mixture was diluted with EA (150 mL) and filtered. The filtrate was washed with brine (60 mL x 5), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EA/PE = 1/5 to 1/2) to give 1-methyl-1H-indazole-5-carbaldehyde (0.8 g, yield 72%) as a yellow solid and 2-methyl-2H-indazole-5-carbaldehyde (0.3 g, 28%) as a white solid.

[0466] INT B32a, 1-methyl-1H-indazole-5-carbaldehyde: LC-MS (ESI): mass calcd. for $C_9H_8N_2O$, 160.08; m/z found, 161.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.42 (s, 1H), 8.32 (s, 1H), 7.87 (dd, J = 8.8, 1.2 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 4.10 (s, 3H).

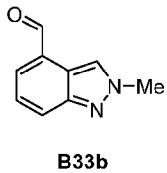
[0467] INT B32b, 2-methyl-2H-indazole-5-carbaldehyde: LC-MS (ESI): mass calcd. for $C_9H_8N_2O$, 160.08; m/z found, 161.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.73 (s, 1H), 8.48 (s, 1H), 7.74 - 7.69 (m, 2H), 4.26 (s, 3H).

Intermediate B33a: 1-methyl-1H-indazole-4-carbaldehyde

Intermediate 33b: 2-methyl-2H-indazole-4-carbaldehyde



B33a



B33b

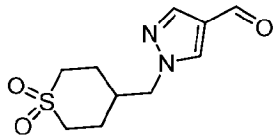
[0468] To a stirred mixture of 1-methyl-1H-indazole-4-carbaldehyde (200 mg, 1.36 mmol, 1.0 eq) in DMF (5.00 mL) were added K_2CO_3 (188 mg, 1.36 mmol, 2.0 eq) and MeI (193 mg, 85.0 µL, 1.36 mmol, 1.0 eq). The resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 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 (PE/EtOAc = 1/1) to give 2-methyl-2H-indazole-4-carbaldehyde

(80.0 mg, yield 36%) as a white solid and 1-methyl-1H-indazole-4-carbaldehyde (110 mg, yield 50%) as a white solid.

[0469] INT 33a: 1-methyl-1H-indazole-4-carbaldehyde: LC-MS (ESI): mass calcd. for $C_9H_8N_2O$, 160.06; m/z found, 161.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.52 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 7.0 Hz, 1H), 7.70 (dd, J = 8.4, 7.0 Hz, 1H), 4.18 (s, 3H).

[0470] INT 33b: 2-methyl-2H-indazole-4-carbaldehyde: LC-MS (ESI): mass calcd. for $C_9H_8N_2O$, 160.06; m/z found, 161.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 8.80 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.84 (t, J = 7.0 Hz, 1H), 7.50 (dd, J = 8.6, 7.0 Hz, 1H), 4.27 (s, 3H).

Intermediate B34: 1-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl)-1H-pyrazole-4-carbaldehyde



Step A: (1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl methanesulfonate

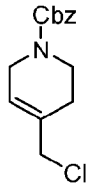
[0471] To a solution of 4-(hydroxymethyl)tetrahydro-2H-thiopyran 1,1-dioxide (200 mg, 1.22 mmol, 1.0 eq) and TEA (185 mg, 255 μL, 1.83 mmol, 1.5 eq) in DCM (5.00 mL) was added dropwise MsCl (181 mg, 123 μL, 1.58 mmol, 1.3 eq) under N_2 at 0 °C and the mixture was stirred at 0 °C for 2 h. The mixture was poured into water (6 mL) and extracted with DCM (20 mL x 3). The organic layer was washed with brine (20 mL x 4), dried over anhydrous $MgSO_4$, and filtered. The fitrate was concentrated under reduced pressure to give crude product (1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl methanesulfonate (150 mg, yield 52%) as a white solid. The crude product was directly used in next step without further purification. LC-MS (ESI): mass calcd. for $C_7H_{14}O_5S_2$, 242.02; m/z found, no Mass.

Step B: 1-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl)-1H-pyrazole-4-carbaldehyde

[0472] To a solution of (1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl methanesulfonate (150 mg, 619 μmol, 1.0 eq) and Cs_2CO_3 (504 mg, 1.55 mmol, 2.5 eq) in DMF (5.0 mL) was added 1H-pyrazole-4-carbaldehyde (71.4 mg, 743 μmol, 1.2 eq). The mixture was stirred at 25 °C for 16 h. After filtration, the filtrate was diluted with water (15 mL) and extracted with EtOAc (10 mL x 3). The organic layer was washed with brine (15 mL x 4), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified

by Prep-TLC (DCM/MeOH = 10 / 1) to obtain 1-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl)-1H-pyrazole-4-carbaldehyde (50.0 mg, yield 30%) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{10}H_{14}N_2O_3S$, 242.07; m/z found, 243.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.46 (s, 1H), 8.03 (s, 1H), 4.17 (d, J = 7.2 Hz, 2H), 3.12 - 3.07 (m, 4H), 1.85 - 1.82 (m, 2H), 1.70 - 1.60 (m, 3H).

Intermediate B35: benzyl 4-(chloromethyl)-3,6-dihydropyridine-1(2H)-carboxylate



Step A: benzyl 4-methylenepiperidine-1-carboxylate

[0473] A solution of tert-butyl 4-methylenepiperidine-1-carboxylate (25 g, 126.9 mmol) was stirred in TFA/CH_2Cl_2 (v/v=1:5) for 2 h at room temperature and concentrate in vacuo. The corresponding amine (12.3 g, 126.8 mmol, 1.0 equiv) was dissolved in THF and K_2CO_3 (52.6 g, 380.4 mmol, 3.0 equiv) and benzyl chloroformate (19.6 mL, 139.5 mmol, 1.10 equiv) were added. The reaction mixture was allowed to stir at 23 °C overnight. To the resulting suspension was added with sat aq. $NaHCO_3$ solution and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude products were purified by column chromatography on silica gel to give the title compound (19.0 g, 76.9 mmol, 80% yield).

[0474] ^1H NMR (400 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H), 5.15 (s, 2H), 4.76 (s, 2H), 3.51 (m, 4H), 2.20 (m, 4H).

Step B: benzyl 2-hydroxy-4-methylenepiperidine-1-carboxylate

[0475] Selenium dioxide (7.9 g, 71.4 mmol, 0.55 eq) was suspended in DCM (750 mL), before t-butyl-hydroperoxide (24.6 g, 272.8 mmol, 2.10 eq) was added and the mixture was stirred for 30 min at 0 °C. Benzyl 4-methylenepiperidine-1-carboxylate (30.0 g, 129.9 mmol, 1 eq) in DCM (100 mL) was added to the mixture and stirred for 1 hr at 0 °C, and further 18 h at 20 °C. Ice chips and 10% w/v sodium bisulfite (450 mL) was added to the solution. The aqueous layer was extracted with DCM (150 mL x 3) and the combined organic layer was washed with brine (200 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified through silica gel column chromatography (ethyl acetate in petroleum ether). The desired product benzyl 2-hydroxy-4-methylenepiperidine-1-carboxylate (19.0 g, 76.9 mmol, 50% yield) was obtained as a light yellow oil.

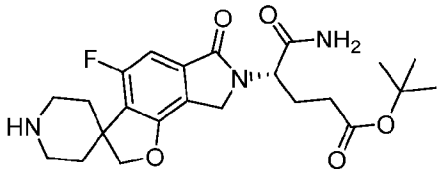
[0476] ^{1}H NMR (400 MHz, CDCl3): δ 7.44-7.29 (m, 5H), 5.15 (s, 2H), 5.04 (s, 1H), 4.89 (d, *J* = 1.9 Hz, 1H), 4.11 (s, 1H), 3.78 (m, 1H), 3.58 (s, 1H), 3.45-3.31 (m, 2H), 2.56-2.06 (m, 2H).

Step C: benzyl 4-(chloromethyl)-3,6-dihydropyridine-1(2H)-carboxylate

[0477] The solution of benzyl 2-hydroxy-4-methylenepiperidine-1-carboxylate (19 g, 76.9 mmol, 1 eq) and K_2CO_3 (11.7 g, 84.6 mmol, 1.10 eq) in toluene (225 mL) was degassed and purged with Ar. $SOCl_2$ (10.1 g, 84.6 mmol, 1.10 eq) was added in one portion at 0 °C, before the reaction temperature was increased to 40 °C and stirred for further 40 min. The reaction mixture was cooled to 0 °C and washed with pre-cooled (0 °C) 1N HCl (150 mL x 2), HCl (0.1 N, 150 mL x 2), H_2O (150 mL x 2), brine (150 mL x 2) and dried with Na_2SO_4, filtered and concentrated in vacuo. Benzyl 4-(chloromethyl)-3,6-dihydropyridine-1(2H)-carboxylate (16 g, 60.4 mmol, 70% yield) was obtained as a yellow oil.

[0478] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H), 5.77 (d, *J* = 23.1 Hz, 1H), 5.15 (s, 2H), 4.01 (m, 4H), 3.62 (m, 2H), 2.23 (m, 2H).

Intermediate B36: tert-butyl (S)-5-amino-4-(4-fluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)-5-oxopentanoate



Step A: 4-bromo-3-fluoro-5-methoxybenzoic acid

[0479] CH_3ONa (30% in MeOH, 1.6 g, 2.0eq.) at rt. was added to a solution of 4-bromo-3,5-difluorobenzoic acid (1.0 g, 1.0eq.) in DMF (30 mL). The reaction mixture was stirred overnight at 60 °C. After cooled to room temperature and ice water (150 mL) was added, then was treated with 2N HCl until pH = 3-4. The reaction was extracted with EtOAc for three times, washed with brine and dried with anhydrous sodium sulfate. And concentrated to afford the title compound (1.0 g) as a solid, which was used in next step without further purification.

Step B: 4-bromo-3-fluoro-5-hydroxybenzoic acid

[0480] To a solution of 4-bromo-3-fluoro-5-methoxybenzoic acid (1.0 g, 1.0 eq.) in dry DCM (40 mL) was cooled down to -78 °C, then added BBr_3 (5.4 g, 5.0 eq.) dropwise during 10 min and stirred at -78 °C for 1 h. The reaction mixture was stirred overnight at rt. After was cooled down to -78 °C, then added saturated ammonium chloride solution dropwise during 30 min. And concentrated to afford the title compound (0.9 g), which was used in next step without further purification.

Step C: methyl 4-bromo-3-fluoro-5-hydroxybenzoate

[0481] Conc. H_2SO_4 (0.6 g, 1.5 eq.) at rt. was added to a solution of 4-bromo-3-fluoro-5-hydroxybenzoic acid (0.9 g, 1.0 eq.) in MeOH (30 mL). The reaction mixture was stirred overnight at 70°C. After cooled to room temperature and ice water (100 mL) was added. The reaction was extracted with EtOAc for three times, washed with brine and dried with anhydrous sodium sulfate. And concentrated to afford the title compound **4** (1.0 g) as a solid, which was used in next step without further purification.

Step D: methyl 4-bromo-5-fluoro-2-formyl-3-hydroxybenzoate

[0482] To a solution of methyl 4-bromo-3-fluoro-5-hydroxybenzoate (249 mg, 1 mmol, 1 eq.) in TFA (5 mL) was added HMTA (560 mg, 4 mmol, 4 eq.) at 20 °C. The mixture was stirred at 125 °C for 12 h. TLC (Petroleum ether/Ethyl acetate = 5/1) indicated starting materials was consumed completely and there was desired product. The mixture was quenched with 2N HCl (5 V) and a yellow solid formed. The mixture was stirred for 10 mins and then additional water (5 V) was added and stirred for 1 hr. The mixture was filtered. The filter cake was dissolved in DCM and filtered on celite, dried and then remove most of the solvent in vacuo. The title compound (138 mg, 0.5 mmol, 50% yield) was obtained as a gray solid, which was indicated by ^{1}H NMR.

[0483] ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.30 (s, 1H), 10.61 (s, 1H), 7.31 (d, J = 8.5 Hz, 1H), 3.97 (s, 3H). LC- MS (m/z): $[M - H]^+$ = 274.99.

Step E: tert-butyl (S)-5-amino-4-(5-bromo-6-fluoro-4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate

[0484] tert-Butyl (*S*)-4,5-diamino-5-oxopentanoate (212 mg, 1.05 mmol, 1.05 eq, HCl) was added in MeOH (5 mL) at 20 °C, then DIEA (1.05 mmol, 1.05 eq), methyl 4-bromo-5-fluoro-2-formyl-3-hydroxybenzoate (277 mg,1 mmol, 1 eq) and AcOH (1.5 mmol, 1.5 eq) were added to the mixture at the same temperature. After 1.5 h, add $NaBH_3CN$ (2 mmol, 2 eq) to the mixture in portions and stirred the mixture at 20 °C for 3 h. After the reaction completed, the reaction mixture was quenched by addition H_2O at 20 °C, and then concentrated under reduced pressure to remove MeOH. Then the mixture was extracted with EtOAc, the combined organic layers were washed with brine (200 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/1 to Ethyl acetate). The title compound (202 mg, 0.47 mmol, 47% yield) was obtained as a yellow solid. LC-MS (m/z): $[M + H]^+$ = 453.28.

Step F: Synthesis of benzyl (S)-4-(((2-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-6-fluoro-1-oxoisoindolin-4-yl)oxy)methyl)-3,6-dihydropyridine-1(2H)-carboxylate

[0485] tert-Butyl (*S*)-5-amino-4-(5-bromo-6-fluoro-4-hydroxy-1-oxoisoindolin-2-yl)-5-oxopentanoate (202 mg, 0.47 mmol, 1 eq), benzyl 4-(chloromethyl)-3,6-dihydropyridine-1(2H)-carboxylate (Compound **A**, 280 mg, 0.49 mmol, 1.05 eq) and K_2CO_3 (194 mg, 1.41 mmol, 3 eq) were added in DMF (5 mL) at 20 °C. Then stir the mixture at 60 °C for 12 h. After the reaction completed, the mixture was concentrated under reduced pressure to give a residue, which was added water (20 mL). The product was extracted with DCM (20 mL x 3). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel to afford the title compound as a yellow solid (204 mg, 66% yield). LC-MS (m/z): $[M + H]^+ = 682.40$.

Step G: benzyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-4-fluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate

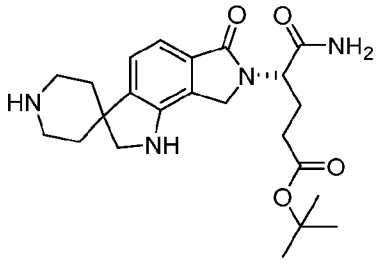
[0486] Benzyl (*S*)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-4-fluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (660 mg, 1 mmol, 1 eq), Bu_3SnH (1228 mg, 4 mmol) and AIBN (16.4 mg, 0.1 mmol, 0.1 eq) were added in toluene (5 mL) at 20 °C and then stir the mixture at 110 °C for 12 h. After the reaction completed, the mixture was quenched by addition saturated potassium fluoride solution and stirred for 1h. The product was extracted with EA. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel to afford the title compound as a yellow solid (400 mg, 69% yield).

[0487] ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H), 7.04 (d, J = 8.4 Hz, 1H), 6.50 (s, 1H), 5.62 (s, 1H), 5.16 (s, 2H), 4.87 (dd, J = 8.9, 6.1 Hz, 1H), 4.56 (s, 2H), 4.47 (d, J = 17.2 Hz, 1H), 4.35 (s, 1H), 4.25 (s, 2H), 2.84 (s, 2H), 2.37 – 2.16 (m, 6H), 1.75 (m, 2H), 1.40 (s, 9H).

Step H: tert-butyl (S)-5-amino-4-(4-fluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)-5-oxopentanoate

[0488] To a 100 mL flask equipped with a magnetic stirring bar was added benzyl (S)-7-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-4-fluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-1'-carboxylate (200 mg), MeOH (10 mL) , and then added 10% Pd/C (20 mg) . Followed by flushing flask with hydrogen, a balloon with hydrogen was attached and the reaction mixture was stirred for 2 h. Upon full consumption of the starting material by TLC monitoring (DCM:MeOH =10:1), the reaction mixture was filtered through celite and washed through with additional MeOH. Solvent was removed and the residual tert-butyl (S)-5-amino-4-(4-fluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)-5-oxopentanoate (120 mg,) as a white solid was used directly in the next step.

Intermediate B37: tert-butyl (S)-5-amino-5-oxo-4-(6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)pentanoate



Step A: 4-bromo-2-methyl-3-nitrobenzoic acid

[0489] Fuming nitric acid (20 mL) was added dropwise to a 0 °C solution of 4-bromo-2-methylbenzoic acid (20.0 g, 93.4 mmol) in concentrated sulfuric acid (80 mL). The reaction mixture was stirred at 55 °C overnight and poured onto ice (~400 mL) and was extracted with EtOAc (3 × 100 mL). The extracts were washed with brine (2 × 50 mL), dried over $NaSO_4$, filtered, and concentrated to give compound **2** (25.0 g, crude). The material was used without further purification.

Step B: methyl 4-bromo-2-methyl-3-nitrobenzoate

[0490] Concentrated sulfuric acid (16.4 g, 167 mmol) was added dropwise to a 0 °C solution of 4-bromo-2-methyl-3-nitrobenzoic acid (25.0 g, crude) in MeOH (150 mL). The reaction mixture was stirred at 90 °C overnight, solvent was removed under vacuum, EtOAc (100 mL) and sat. aq. $NaHCO_3$ (200 mL) was added. The products were extracted with EtOAc (50 mL x 3), and the combined organic extracts were washed with brine, dried over $NaSO_4$, filtered, and concentrated in vacuo to give the title compound (12.0 g, crude). The residue was used in the next step without further purification.

Step C: methyl 4-bromo-2-(bromomethyl)-3-nitrobenzoate

[0491] To a solution of **3** (12.0 g, 44.0 mmol) in DCE (200 mL) were added NBS (10.5 g, 58.8 mmol) and AIBN (0.722 g, 4.40 mmol) at room temperature. The mixture was stirred at 90 °C under N_2 for 6 h. The mixture was poured into aq. $Na_2S_2O_3$ at room temperature and extracted with EtOAc. The organic layer was separated, washed with satd. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography to give the title compound (2.90 g) as a white solid.

[0492] ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 4.82 (s, 2H), 3.92 (s, 3H).

Step D: tert-butyl 5-amino-4-(5-bromo-4-nitro-1-oxoisoindolin-2-yl)-5-oxopentanoate

[0493] To a solution of methyl 4-bromo-2-(bromomethyl)-3-nitrobenzoate (2.90 g, 8.22 mmol) in ACN (50 mL) was added tert-butyl (S)-4,5-diamino-5-oxopentanoate (2.94 g, 12.3 mmol) and DIEA (3.18 g, 24.7 mmol). The resulting mixture was stirred at 90 °C overnight, solvent was removed under vacuum, EtOAc (30 mL) and H_2O (50 mL) was added. The products were extracted with EtOAc (30 mL x 3), and the combined organic extracts were washed with brine, dried over $NaSO_4$, filtered, and concentrated. The residue was purified by column chromatography to give the title compound (2.48 g).

Step E: tert-butyl 5-amino-4-(4-amino-5-bromo-1-oxoisoindolin-2-yl)-5-oxopentanoate

[0494] To a solution of tert-butyl 5-amino-4-(5-bromo-4-nitro-1-oxoisoindolin-2-yl)-5-oxopentanoate (2.48 g, 5.62 mmol) in EtOH/H_2O (40 mL/4 mL) was added Fe (1.57 g, 28.1 mmol) and NH_4Cl (0.894 g, 16.9 mmol). The resulting mixture was stirred at 70 °C overnight then filtered through glass fiber filter paper on a Buchner funnel to remove the iron. The solid was rinsed with EtOH and the filtrate was concentrated and partitioned between EtOAc and H_2O (50 mL/50 mL). The aqueous layer was separated and washed with EtOAc (2×50 mL). The combined organic extracts were washed with brine (50 mL), dried over $NaSO_4$, filtered and concentrated. The residue was purified by column chromatography to give the title compound (1.74 g).

[0495] ^{1}H NMR (600 MHz, DMSO) δ 7.55 (s, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.18 (s, 1H), 6.83 (d, J = 7.9 Hz, 1H), 5.66 (s, 2H), 4.71 (dd, J = 10.6, 3.8 Hz, 1H), 4.47 (d, J = 17.8 Hz, 1H), 4.26 (d, J = 17.8 Hz, 1H), 2.21 – 2.11 (m, 2H), 1.33 (s, 9H).

Step F: benzyl 4-(((2-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-1-oxoisoindolin-4-yl)amino)methyl)-3,6-dihydropyridine-1(2H)-carboxylate

[0496] To a solution of tert-butyl 5-amino-4-(4-amino-5-bromo-1-oxoisoindolin-2-yl)-5-oxopentanoate (0.840 g, 2.04 mmol) in CH_3CN (20 mL) was added benzyl 4-(chloromethyl)-3,6-dihydropyridine-1(2H)-carboxylate (0.812 g, 3.07 mmol), DIEA (0.789 g, 6.12 mmol) and KI (0.510 g, 3.07 mmol). The resulting mixture was stirred at 70 °C overnight, solvent was removed under vacuum, EtOAc (10 mL) and H_2O (50 mL) was added. The products were extracted with EtOAc (20 mL x 3), and the combined organic extracts were washed with brine, dried over $NaSO_4$, filtered, and concentrated. The residue was purified by column chromatography to give the title compound (910 mg).

Step G: benzyl 7'-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-6'-oxo-1',6',7',8'-tetrahydro-2'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indole]-1-carboxylate

[0497] Benzyl 4-(((2-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-5-bromo-1-oxoisoindolin-4-yl)amino)methyl)-3,6-dihydropyridine-1(2H)-carboxylate (1.30 g, 2.03

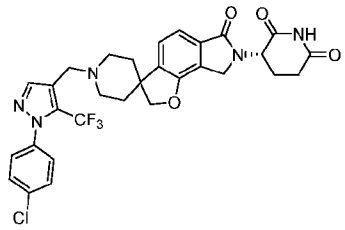
mmol), Bu3SnH (2.36 g, 8.12 mmol) and AIBN (333 mg, 2.03 mmol) were added in toluene (40 mL) at 20 °C and then stir the mixture at 110 °C for 12 h. After the reaction completed, the mixture was quenched by addition saturated potassium fluoride solution and stirred for 1h. The product was extracted with EA. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the title compound (500 mg).

[0498] ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.40 – 7.35 (m, 4H), 7.34 – 7.30 (m, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 5.15 (s, 2H), 4.95 (dd, J = 10.1, 4.5 Hz, 1H), 4.51 (d, J = 17.2 Hz, 1H), 4.35 (d, J = 17.2 Hz, 1H), 4.12 (dq, J = 14.3, 2.7 Hz, 2H), 3.62 – 3.55 (m, 2H), 3.02 (brs, 2H), 2.31 – 2.17 (m, 4H), 1.86 – 1.65 (m, 4H), 1.38 (s, 9H).

Step H: tert-butyl (S)-5-amino-5-oxo-4-(6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)pentanoate

[0499] To a 100 mL flask equipped with a magnetic stirring bar was added benzyl 7'-(1-amino-5-(tert-butoxy)-1,5-dioxopentan-2-yl)-6'-oxo-1',6',7',8'-tetrahydro-2'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indole]-1-carboxylate (65 mg), THF (5 mL), and then 10% Pd/C (10 mg). The flask was evacuated and flushed three times with hydrogen, and the reaction mixture was stirred for 2 h under hydrogen atmosphere (balloon). Upon full consumption of the starting material by TLC monitoring, the reaction mixture was filtered through celite and washed through with additional MeOH. Solvent was removed and the residual tert-butyl (S)-5-amino-5-oxo-4-(6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)pentanoate was obtained (45 mg) as a white solid which was used directly in the next step.

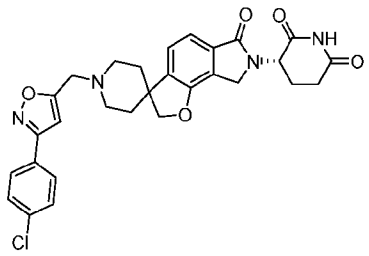
Compound B1: (S)-3-(1'-((1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl) methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione



[0500] To a suspension of (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B2**, 50.0 mg, 128 μmol, 1.0 eq) in MeOH (10.0 mL) was added Diisopropylethylamine (165 mg, 220 μL, 1.28 mmol, 10.0 eq) at room temperature. After 5-10 min, 1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-

carbaldehyde (**Intermediate B12**, 52.6 mg, 191 μmol, 1.5 eq) and Acetic acid (76.6 mg, 73.3 μL, 1.28 mmol, 10.0 eq) were added to above mixture at room temperature (pH ~6). The reaction mixture was stirred at 25 °C for 4 h. Then Sodium cyanoborohydride (16.0 mg, 255 μmol, 2.0 eq) was added and the resulting reaction mixture was stirred at 25 °C for 1 h. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-TLC (DCM/MeOH = 10/1) to give impure product as a white solid. The impure product was further purified by Prep-HPLC with YMC-Actus Triart C18 (5 μm, 250 x 21 mm), and mobile phase of 5-95% ACN in water (0.1% FA) over 10 min and then hold at 100% ACN for 3 min, at a flow rate of 20 mL/min to give (S)-3-(1'-((1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazol-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 (6.50 mg, yield 8%) as a white solid. as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{27}ClF_3N_5O_4$, 613.17; m/z found, 614.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 7.90 (s, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 5.11 - 5.07 (m, 1H), 4.55 (s, 2H), 4.39 (d, J = 17.0 Hz, 1H), 4.22 (d, J = 17.0 Hz, 1H), 3.59 (s, 2H), 2.95 - 2.86 (m, 3H), 2.61 - 2.57 (m, 1H), 2.45 - 2.37 (m, 1H), 2.16 - 2.08 (m, 2H), 2.00 - 1.94 (m, 3H), 1.75 - 1.72 (m, 2H).

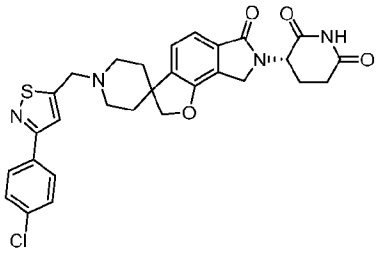
Compound B2: (S)-3-(1'-((3-(4-chlorophenyl)isoxazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0501] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B2**) and 3-(4-chlorophenyl)isoxazole-5-carbaldehyde (**Intermediate B13**) as a white solid. LC-MS (ESI): mass calcd for: $C_{29}H_{27}ClN_4O_5$, 546.17; m/z found, 547.3 $[M+H]^+$. ^1H NMR(400 MHz, DMSO) δ 10.97 (s, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 7.2 Hz, 1H), 7.28 (d, J = 7.4 Hz, 1H), 7.04 (s, 1H), 5.11 - 5.06 (m, 1H), 4.53 (s, 2H), 4.38 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 3.79 (s, 2H), 2.92 - 2.88 (m, 3H), 2.61 - 2.56 (m, 1H), 2.44 -

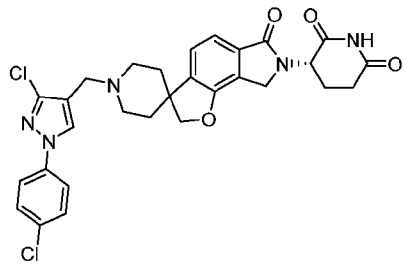
2.38 (m, 1H), 2.20 (t, J = 12.2 Hz, 2H), 1.98 (d, J = 7.6 Hz, 3H), 1.70 (t, J = 10.6 Hz, 2H).

Compound B3: (S)-3-(1'-((3-(4-chlorophenyl)isothiazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0502] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione **(Intermediate B2)** and 3-(4-chlorophenyl)isothiazole-5-carbaldehyde **(Intermediate B14)** as a white solid. LC-MS (ESI): mass calcd. for $C_{29}H_{27}ClN_4O_4S$, 562.1; m/z found, 563.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.85 (s, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 5.11 - 5.06 (m, 1H), 4.58 - 4.50 (m, 2H), 4.38 (d, J = 17.2 Hz, 1H), 4.22 (d, J = 17.2 Hz, 1H), 3.96 (s, 2H), 2.98 - 2.85 (m, 3H), 2.61 - 2.56 (m, 1H), 2.43 - 2.39 (m, 1H), 2.22 (t, J = 11.6 Hz, 2H), 1.96 (t, J = 12.4 Hz, 3H), 1.73 (t, J = 11.4 Hz, 2H).

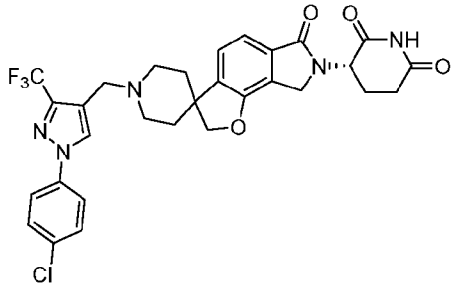
Compound B4: (S)-3-(1'-((3-chloro-1-(4-chlorophenyl)-1H-pyrazol-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0503] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione **(Intermediate B2)** and 3-chloro-1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde **(Intermediate B15)** as a white solid. LC-MS (ESI): mass calcd for: $C_{29}H_{27}Cl_2N_5O_4$ 579.1; m/z found, 580.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.61 (s, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 7.37

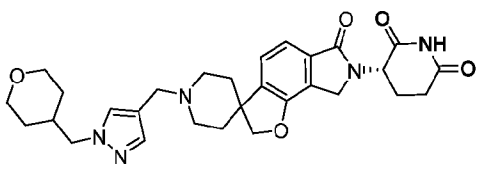
(d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 5.10 - 5.05 (m, 1H), 4.60 - 4.45 (m, 2H), 4.38 (d, J = 17.0 Hz, 1H), 4.21 (d, J = 17.0 Hz, 1H), 3.45 (s, 2H), 2.90 - 2.87 (m, 3H), 2.60 - 2.56 (m, 1H), 2.46 - 2.36 (m, 1H), 2.09 (t, J = 11.7 Hz, 2H), 1.98 - 1.89 (m, 3H), 1.70 (t, J = 11.0 Hz, 2H).

Compound B5: (S)-3-(1'-((1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-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



[0504] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B2**) and 1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde (**Intermediate B16**) as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{27}ClF_3N_5O_4$, 613.2; m/z found, 614.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.70 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 5.10 - 5.06 (m, 1H), 4.54 (s, 2H), 4.38 (d, J = 17.0 Hz, 1H), 4.21 (d, J = 17.0 Hz, 1H), 3.55 (s, 2H), 2.98 - 2.83 (m, 3H), 2.60 - 2.56 (m, 1H), 2.44 - 2.35 (m, 1H), 2.15 - 2.04 (m, 2H), 2.01 - 1.86 (m, 3H), 1.77 - 1.65 (m, 2H).

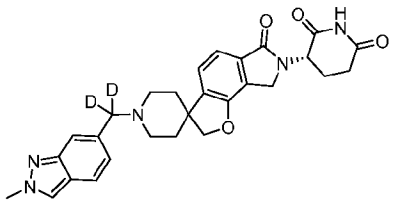
Compound B6: (S)-3-(6-oxo-1'-((1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0505] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-

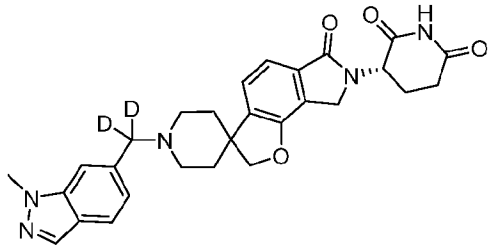
e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B2**) and 1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazole-4-carbaldehyde (**Intermediate B17**) as a white solid. LC-MS (ESI): mass calcd. for $C_{29}H_{35}N_5O_5$, 533.0; m/z found, 534.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.16 (s, 1H), 7.61 (s, 1H), 7.40 - 7.34 (m, 2H), 7.26 (d, J = 7.6 Hz, 1H), 5.09 - 5.05 (m, 1H), 4.49 (s, 2H), 4.37 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 3.96 (d, J = 7.2 Hz, 2H), 3.83 - 3.80 (m, 2H), 3.41 (s, 2H), 3.24 (dd, J = 11.6, 9.6 Hz, 2H), 2.94 - 2.81 (m, 3H), 2.64 - 2.59 (m, 1H), 2.46 - 2.34 (m, 1H), 2.04 - 1.89 (m, 5H), 1.68 (t, J = 10.8 Hz, 2H), 1.36 (d, J = 10.8 Hz, 2H), 1.27 - 1.14 (m, 3H).

Compound B7: (S)-3-(1'-((2-methyl-2H-indazol-6-yl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



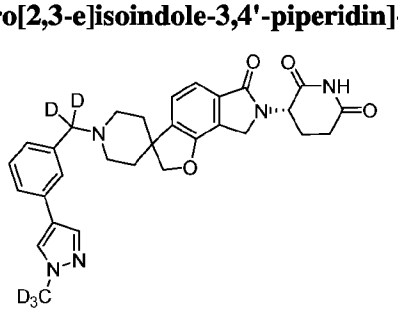
[0506] To a solution of (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B2**, 13.0 mg, 36.7 μmol, 1.0 eq) in DMF (1.0 mL) was added N-ethyl-N-isopropylpropan-2-amine (14.2 mg, 110 μmol, 3.0 eq) at 0 °C and the mixture was stirred at 0 °C for 15 min. Then 6-(bromomethyl-d_2)-2-methyl-2H-indazole (**Intermediate B18**, 10.0 mg, 44.0 μmol, 1.2 eq) was added to above mixture and the reaction mixture was stirred at 25 °C for 30 min. After evaporation, the residue was purified with Prep-HPLC with YMC-Actus Triart C18 (5 um, 20 x 250 mm), and mobile phase of 5-95% ACN in water (0.1% HCOOH) over 20 min and then hold at 100% ACN for 2 min, at a flow rate of 25 mL/min to give (S)-3-(1'-((2-methyl-2H-indazol-6-yl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione formate (8.0 mg, yield 43%) as a white solid. LC-MS (ESI): mass calcd. for $C_{28}H_{27}D_2N_5O_4$, 501.58; m/z found, 502.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.27 (s, 1H), 8.15 (s, 1H), 7.64 (dd, J = 8.6, 0.8 Hz, 1H), 7.47 (d, J = 0.8 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.05 (dd, J = 8.6, 1.2 Hz, 1H), 5.10 - 5.05 (m, 1H), 4.57 - 4.50 (m, 2H), 4.37 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 4.14 (s, 3H), 2.97 - 2.80 (m, 3H), 2.60 - 2.56 (m, 1H), 2.45 - 2.33 (m, 1H), 2.14 - 2.00 (m, 2H), 2.00 - 1.87 (m, 3H), 1.68 (t, J = 11.2 Hz, 2H).

Compound B8: (S)-3-(1'-((1-methyl-1H-indazol-6-yl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0507] The title compound was prepared according to the procedure described in Compound B-7 by displacement between (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione **(Intermediate B2)** and 6-(bromomethyl-d2)-1-methyl-1H-indazole **(Intermediate B19)** as a white solid. LC-MS (ESI): mass calcd. for $C_{28}H_{27}D_2N_5O_4$, 501.58; m/z found, 502.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.14 (s, 1H), 8.00 (d, J = 0.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.54 (s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.16 (dd, J = 8.4, 1.2 Hz, 1H), 5.10 - 5.05 (m, 1H), 4.58 - 4.49 (m, 2H), 4.38 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 4.04 (s, 3H), 2.98 - 2.81 (m, 3H), 2.60 - 2.56 (m, 1H), 2.45 - 2.32 (m, 1H), 2.10 (t, J = 11.6 Hz, 2H), 1.98 - 1.91 (m, 3H), 1.69 (t, J = 11.0 Hz, 2H).

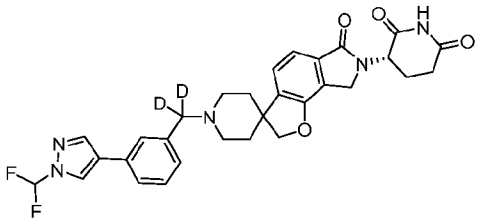
Compound B9: (S)-3-(1'-((3-(1-(methyl-d3)-1H-pyrazol-4-yl)phenyl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0508] The title compound was prepared according to the procedure described in Compound B-7 by displacement between (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione **(Intermediate B2)** and 4-(3-(bromomethyl-d2)phenyl)-1-(methyl-d3)-1H-pyrazole **(Intermediate B20)** as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{26}D_5N_5O_4$, 530.27; m/z found, 531.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.15 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.49 (s, 1H), 7.43 (dd, J = 12.0, 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 5.10 - 5.06 (m, 1H), 4.53 (s, 2H), 4.38 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 2.95 -

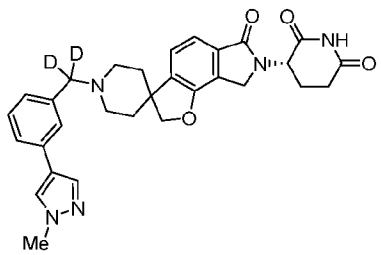
2.81 (m, 3H), 2.61 - 2.56 (m, 1H), 2.43 - 2.36 (m, 1H), 2.06 (t, *J* = 11.6 Hz, 2H), 2.01 - 1.87 (m, 3H), 1.69 (t, *J* = 11.2 Hz, 2H).

Compound B10: (S)-3-(1'-((3-(1-(difluoromethyl)-1H-pyrazol-4-yl) phenyl) methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione



[0509] The title compound was prepared according to the procedure described in Compound B-7 by displacement between (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B2**) and 4-(3-(bromomethyl-d2)phenyl)-1-(difluoromethyl)-1H-pyrazole (**Intermediate B21**) as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{27}D_2F_2N_5O_4$, 563.23; m/z found, 564.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.73 (s, 1H), 8.28 (s, 2H), 7.83 (t, *J* = 59.2 Hz, 1H), 7.64 (s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.39 (dd, *J* = 17.4, 7.6 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 2H), 5.10 - 5.05 (m, 1H), 4.56 - 4.50 (m, 2H), 4.38 (d, *J* = 17.21 Hz, 1H), 4.21 (d, *J* = 17.2 Hz, 1H), 2.96 - 2.88 (m, 1H), 2.85 (d, *J* = 10.4 Hz, 2H), 2.62 - 2.55 (m, 1H), 2.47 - 2.36 (m, 1H), 2.07 (t, *J* = 11.8 Hz, 2H), 2.01 - 1.89 (m, 3H), 1.69 (t, *J* = 11.4 Hz, 2H).

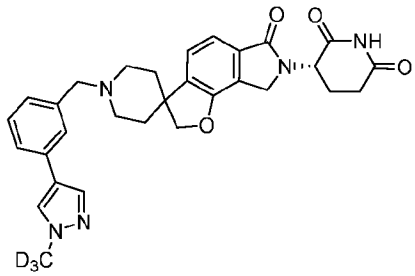
Compound B11: (S)-3-(1'-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0510] The title compound was prepared according to the procedure described in Compound B-7 by displacement between (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B2**) and 4-(3-(bromomethyl-d2)phenyl)-1-methyl-1H-pyrazole (**Intermediate B22**) as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{29}D_2N_5O_4$, 527.25; m/z found, 528.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6)

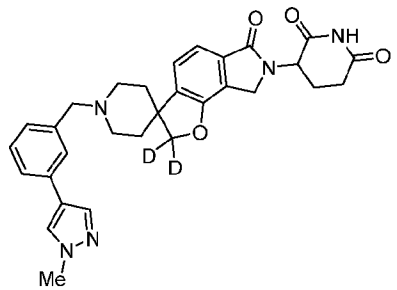
δ 10.96 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.51 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.33 (s, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 5.10 - 5.06 (m, 1H), 4.54 (s, 2H), 4.38 (d, *J* = 17.2 Hz, 1H), 4.21 (d, *J* = 17.2 Hz, 1H), 3.87 (s, 3H), 2.97 - 2.84 (m, 3H), 2.61 - 2.56 (m, 1H), 2.45 - 2.32 (m, 1H), 2.14 - 2.11 (m, 2H), 1.99 - 1.92 (m, 3H), 1.71 (t, *J* = 11.6 Hz, 2H).

Compound B12: (S)-3-(1'-(3-(1-(methyl-d3)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0511] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione **(Intermediate B2)** and 3-(1-(methyl-d3)-1H-pyrazol-4-yl)benzaldehyde **(Intermediate B23)** as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{28}D_3N_5O_4$, 528.26; m/z found, 529.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.14 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.50 (s, 1H), 7.43 (dd, *J* = 13.2, 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 5.10 - 5.05 (m, 1H), 4.54 (s, 2H), 4.38 (d, *J* = 17.2 Hz, 1H), 4.21 (d, *J* = 17.2 Hz, 1H), 3.53 (s, 2H), 2.94 - 2.83 (m, 3H), 2.60 - 2.56 (m, 1H), 2.43 - 2.36 (m, 1H), 2.08 (t, *J* = 11.8 Hz, 2H), 2.08 - 1.90 (m, 3H), 1.69 (t, *J* = 11.4 Hz, 2H).

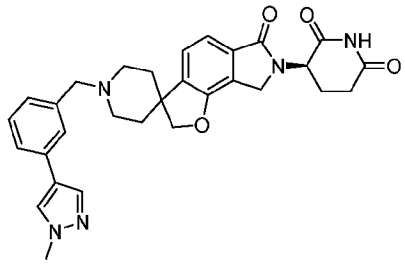
Compound B13: 3-(1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7Hspiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl-2,2-d2)piperidine-2,6-dione



[0512] The title compound was prepared according to the procedure described in Compound

B-1 by reductive amination between (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl-2,2-d2)piperidine-2,6-dione (**Intermediate B3**) and 3-(1-methyl-1H-pyrazol-4-yl)benzaldehyde (**Intermediate B27**) as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{29}D_2N_5O_4$, 527.62; m/z found, 528.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.30 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.50 (s, 1H), 7.43 (dd, J = 11.6, 7.6 Hz, 2H), 7.30 (dd, J = 13.4, 5.8 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 5.10 - 5.05 (m, 1H), 4.38 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 3.87 (s, 3H), 3.52 (s, 2H), 2.98 - 2.79 (m, 3H), 2.560 - 2.56 (m, 1H), 2.44 - 2.32 (m, 1H), 2.06 (t, J = 12.0 Hz, 2H), 2.00 - 1.87 (m, 3H), 1.69 (t, J = 10.8 Hz, 2H).

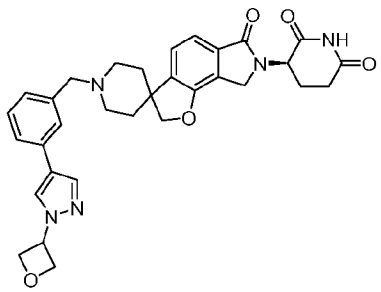
Compound B14: (R)-3-(1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0513] To a suspension of (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione (**Intermediate B2**, 320 mg, 817 μmol, 1.0 eq) in DMF (20.0 mL) was added triethylamine (826 mg, 1.14 mL, 8.17 mmol, 10.0 eq) at room temperature. After 5-10 min, 3-(1-methyl-1H-pyrazol-4-yl) benzaldehyde (**Intermediate B27**, 304 mg, 1.63 mmol, 2.0 eq) and Acetic acid (981 mg, 939 μL, 16.3 mmol, 20.0 eq) were added to above mixture at room temperature (pH ~6). The reaction mixture was stirred at 25 °C for 2 h, and then sodium triacetoxyborohydride (346 mg, 1.63 mmol, 2.0 eq) was added and the resulting reaction mixture was stirred at 25 °C for 2 h. The resulting mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic phases were washed with brine (50 mL x 4), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 50/1 to 15/1 v/v) to provide (S)-3-(1'-(3-(1-methyl-1H-pyrazol-4-yl) benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione (290 mg, yield 86%) (80% e.e.) as a yellow solid. The product was slurred with a mixed solvent of MeOH (10 mL) and MeCN (10 mL), filtered, and the filtrate was concentrated under reduced pressure to give (S)-3-(1'-(3-(1-methyl-1H-pyrazol-

4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**A170**) (130 mg, 95% e.e.). The cake (~100 mg, R/S mixture) was separated by SFC Prep-HPLC with IMADZU PREP SOLUTION SFC with ChiralPak IH (ChiralPak IH, 250 x 21.2 mm I.D., 5 μm), and mobile phase of A for CO_2 and B for ETOH + 0.1% NH_3H_2O 5-99% over 5 h, at a flow rate of 40 mL/min to give(S)-3-(1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (30.0 mg, yield 20.0%, 100% e.e) as a white solid. And (R)-3-(1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (12.7 mg, yield 8.5%, 96.5% e.e.) as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{31}N_5O_4$, 525.24; m/z found, 526.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.49 (s, 1H), 7.46 - 7.40 (m, 2H), 7.33 - 7.26 (m, 2H), 7.16 (d, J = 7.6 Hz, 1H), 5.10 - 5.06 (m, 1H), 4.54 (s, 2H), 4.38 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 3.87 (s, 3H), 3.52 (s, 2H), 2.90 - 2.82 (m, 3H), 2.58 (d, J = 17.8 Hz, 1H), 2.43 - 2.40 (m, 1H), 2.06 - 2.02 (m, 2H), 1.97 - 1.93 (m, 3H), 1.71 - 1.66 (m, 2H).

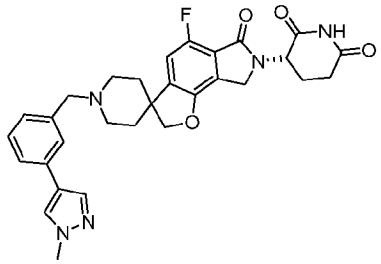
Compound B15: (R)-3-(1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0514] To a stirred mixture of (S)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B2**, 850 mg, 2.17 mmol, 1.0 eq) in MeOH (5.0 mL) was added DIPEA (336.2 mg, 2.6 mmol, 1.2 eq) at room temperature and the mixture was stirred for 15 min. 3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzaldehyde (**Intermediate B28**, 743 mg, 3.25 mmol, 1.5 eq) and AcOH (260.4 mg, 4.34 mmol, 2.0 eq) were added to above mixture and the reaction mixture was stirred at room temperature for 3 h. Then $NaBH_3CN$ (341 mg, 5.42 mmol, 2.5 eq) was added to above mixture and the reaction mixture was stirred at room temperature for 1 h. After evaporation, the residue was purified by flash column chromatography on silica gel (DCM/MeOH = 10/1 v/v) to get a crude product. The crude product was further purified by Prep-HPLC with YMC-Actus Triart 18C (5μm, 20

x 250 mm), and mobile phase of 5-99% ACN in water (0.1% FA) over 10 min and then hold at 100% ACN for 2 min, at a flow rate of 25 mL/min to (S)-3-(1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (650 mg, ~90% e.e., yield 53%). The racemate product was further separated by SFC Prep-HPLC with Waters Thar 80 preparative SFC (ChiralPak IH, 150 × 21.2 mm I.D., 5 μm), and mobile phase of A for CO_2 and B for 0.1% 7 mol/L NH_3 in EtOH over 4 h, at a flow rate of 40 mL/min to get (S)-3-(1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (350 mg, yield 54%) as a white solid and 60 mg of racemate mixture (S/R = 1/1). The racemate mixture (60 mg) was second separated by SFC by SFC Prep-HPLC with Waters Thar 80 preparative SFC (ChiralPak IH, 150 × 21.2 mm I.D., 5 μm), and mobile phase of A for CO_2 and B for 0.1% 7 mol/L NH_3 in EtOH over 4 h, at a flow rate of 40 mL/min to afford (R)-3-(1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (9.6 mg, yield 16%) as a white solid. LC-MS (ESI): mass calced for: $C_{32}H_{33}N_5O_5$ 567.65; m/z found, 568.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.38 (s, 1H), 8.02 (s, 1H), 7.54 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 5.67 - 5.50 (m, 1H), 5.11 - 5.07 (m, 1H), 4.94 (d, J = 7.4 Hz, 4H), 4.54 (s, 2H), 4.38 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 3.52 (s, 2H), 2.97 - 2.76 (m, 3H), 2.59 (d, J = 16.6 Hz, 1H), 2.44 - 2.39 (m, 1H), 2.09 - 2.03 (m, 2H), 1.98 - 1.90 (m, 3H), 1.69 (t, J = 11.4 Hz, 2H).

Compound B16: (S)-3-(5-fluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



Step A: tert-butyl (S)-5-amino-4-(5-fluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)-5-oxopentanoate

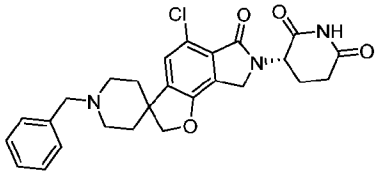
[0515] A solution of tert-butyl (S)-5-amino-4-(5-fluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)-5-oxopentanoate (**Intermediate B4**, 60 mg, 1.0eq.) and 3-(1-methyl-1H-pyrazol-4-yl)benzaldehyde (23 mg, 1.0eq.) in DMAc (3 mL) was

added acetic acid (0.01 mL). The resulting reaction mixture was stirred at ambient temperature for 15 min. Then sodium triacetoxyborohydride (57 mg, 2eq.) was added. The resulting reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with water (100 mL) and extracted with DCM/MeOH = 10:1 (x3). The organic phases were combined and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The resulting crude material was purified by flash chromatography to afford the title product as a white solid (60 mg). LC-MS (m/z): $[M + H]^+ = 618.40$.

Step B: (S)-3-(5-fluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

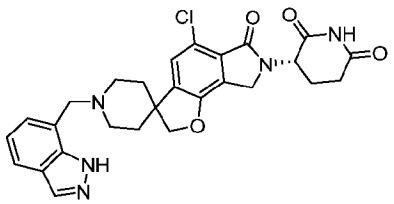
[0516] To the suspension of tert-butyl (S)-5-amino-4-(5-fluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)-5-oxopentanoate (40 mg, 1eq) in ACN (1 mL) was added Benzenesulfonic acid (40 mg, 4 eq). The resulting suspension was stirred at 90°C for 5 h. The reaction mixture was allowed to cool to room temperature and added TFA, then purified by prep-HPLC quickly to afford a white solid as the final product (18 mg). LC-MS (m/z): $[M + H]^+ = 544.40$.

Compound B17: (S)-3-(1'-benzyl-5-chloro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



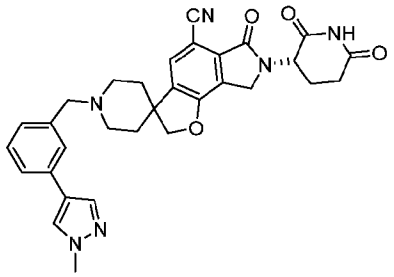
[0517] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (S)-3-(5-chloro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B5**) and benzaldehyde as a white solid. LC-MS (ESI): mass calcd. for $C_{26}H_{26}ClN_3O_4$, 479.2; m/z found, 480.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 10.98 (s, 1H), 8.26 (s, 1H), 7.64 – 7.08 (m, 6H), 5.04 (s, 1H), 4.56 (s, 2H), 4.34 (d, J = 17.2 Hz, 1H), 4.18 (d, J = 17.0 Hz, 1H), 3.50 (s, 2H), 2.90 (s, 1H), 2.79 (s, 2H), 2.60 (s, 1H), 2.40 – 2.37 (m, 1H), 2.07 – 1.88 (m, 5H), 1.68 (s, 2H).

Compound B18: (S)-3-(1'-((1H-indazol-7-yl)methyl)-5-chloro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0518] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (S)-3-(5-chloro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B5**) and 1H-indazole-7-carbaldehyde as a white solid. LC-MS (ESI): mass calced for $C_{27}H_{26}ClN_5O_4$ 519; m/z found, 520.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 10.98 (s, 1H), 8.13 (s, 1H), 8.10 (s, 1H), 7.67 (s, 1H), 7.46 (s, 1H), 7.25 (s, 1H), 7.08 (s, 1H), 5.08 - 5.03 (m, 1H), 4.59 (s, 2H), 4.35 (d, J = 17.4 Hz, 1H), 4.18 (d, J = 17.4 Hz, 1H), 3.82 (s, 2H), 2.93 - 2.85 (m, 3H), 2.62 - 2.56 (m, 1H), 2.47 - 2.43 (m, 1H), 2.18 - 1.91 (m, 5H), 1.68 (s, 2H).

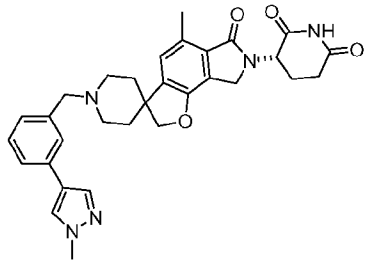
Compound B19: (S)-7-(2,6-dioxopiperidin-3-yl)-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-5-carbonitrile



[0519] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (S)-7-(2,6-dioxopiperidin-3-yl)-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidine]-5-carbonitrile (**Intermediate B6**) and 3-(1-methyl-1H-pyrazol-4-yl)benzaldehyde (**Intermediate B27**) as a white solid. LC-MS (ESI): mass calced for: $C_{31}H_{33}N_5O_4$ 550.23; m/z found, 551.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.28 (s, 1H), 8.14 (s, 1H), 7.99 (s, 1H), 7.85 (s, 1H), 7.50 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 5.11 - 5.07 (m, 1H), 4.68 (s, 2H), 4.45 (d, J = 17.8 Hz, 1H), 4.29 (d, J = 17.8 Hz, 1H), 3.88 (s, 3H), 3.53 (s, 2H), 2.94 - 2.83 (m, 3H), 2.62 - 2.57 (m, 1H), 2.45 - 2.29 (m, 1H), 2.09 - 1.96 (m, 5H), 1.71 (t, J = 11.2 Hz, 2H).

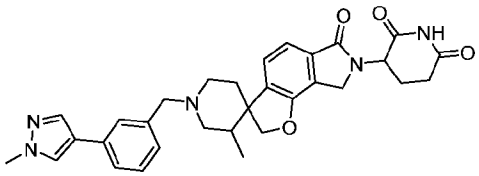
Compound B20: (S)-3-(5-methyl-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-

dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



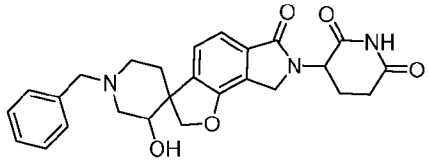
[0520] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (S)-3-(5-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B7**) and 3-(1-methyl-1H-pyrazol-4-yl)benzaldehyde (**Intermediate B27**) as a brown solid. LC-MS (ESI): mass calced for: $C_{31}H_{33}N_5O_4$ 539.3; m/z found, 540.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.33 (s, 1H), 8.14 (s, 1H), 7.85 (s, 1H), 7.50 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 6.0 Hz, 2H), 5.05 - 5.01 (m, 1H), 4.49 (s, 2H), 4.30 (d, J = 17.2 Hz, 1H), 4.14 (d, J = 17.2 Hz, 1H), 3.87 (s, 3H), 3.52 (s, 2H), 2.96 - 2.89 (m, 1H), 2.86 - 2.82 (m, 2H), 2.63 - 2.57 (m, 1H), 2.55 (s, 3H), 2.39 - 2.36 (m, 1H), 2.09 - 2.22 (m, 2H), 1.97 - 1.92 (m, 3H), 1.67 (t, J = 10.4 Hz, 2H).

Compound B21: 3-(3'-methyl-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



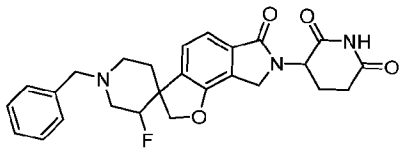
[0521] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between 3-(3'-methyl-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B28**) and 3-(1-methyl-1H-pyrazol-4-yl)benzaldehyde (**Intermediate B27**) as a white solid. LC-MS (ESI): mass calcd. for $C_{31}H_{33}N_5O_4$, 539.64; m/z found, 540.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.13 (d, J = 4.4 Hz, 1H), 7.84 (d, J = 4.8 Hz, 1H), 7.47 (dd, J = 22.8, 8.3 Hz, 2H), 7.39 - 7.26 (m, 3H), 7.16 (d, J = 7.0 Hz, 1H), 5.10 - 5.05 (m, 1H), 4.69 - 4.66 (m, 1H), 4.41 - 4.22 (m, 3H), 3.87 (s, 3H), 3.49 (s, 2H), 2.95 - 2.74 (m, 3H), 2.61 - 2.57 (m, 1H), 2.43 - 2.39 (m, 1H), 2.11 - 1.87 (m, 4H), 1.78 - 1.74 (m, 2H), 0.75 - 0.52 (m, 3H).

Compound B22: 3-(1'-benzyl-3'-hydroxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



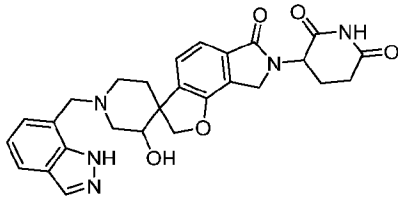
[0522] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between 3-(3'-hydroxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B29**) and benzaldehyde as a white solid. LC-MS (ESI): mass calcd. for $C_{26}H_{27}N_3O_5$, 461.52; m/z found, 462.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 7.38 - 7.23 (m, 7H), 5.08 - 5.04 (m, 1H), 4.95 (s, 1H), 4.77 - 4.75 (m, 1H), 4.45 - 4.31 (m, 2H), 4.19 (d, J = 17.0 Hz, 1H), 3.81 (dd, J = 10.4, 4.4 Hz, 1H), 3.56 (d, J = 13.2 Hz, 1H), 3.44 (d, J = 13.2 Hz, 1H), 2.95 - 2.71 (m, 3H), 2.63 - 2.54 (m, 1H), 2.43 - 2.39 (m, 1H), 2.02 - 1.88 (m, 3H), 1.77 - 1.72 (m, 2H).

Compound B23: 3-(1'-benzyl-3'-fluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



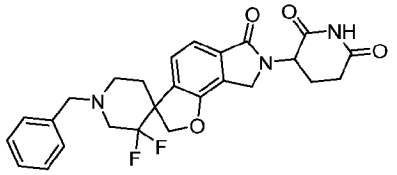
[0523] To a solution of 3-(1'-benzyl-3'-hydroxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Example B-22**, 20.0 mg, 43.3 μmol, 1.0 eq) in DCM (40.0 mL) was added DAST (140 mg, 115 μL, 867 μmol, 20.0 eq) and the reaction mixture was stirred at room temperature overnight. The mixture was washed with saturated aqueous $NaHCO_3$ solution (30 mL x 3) and brine (30 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with Prep-HPLC with YMC-Actus Triart C18 (5 um, 20 x 250 mm), and mobile phase of 5-95% ACN in water (0.1% HCOOH) over 20 min and then hold at 100% ACN for 2 min, at a flow rate of 25 mL/min to afford 3-(1'-benzyl-3'-fluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (10.0 mg, yield 50%) as a white solid. LC-MS (ESI): mass calcd. for $C_{26}H_{26}FN_3O_4$, 463.51; m/z found, 464.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.61 - 7.41 (m, 7H), 5.13 - 5.09 (m, 1H), 5.02 - 4.53 (m, 4H), 4.47 - 4.36 (m, 2H), 4.30 - 4.24 (m, 2H), 3.92 (s, 1H), 3.30 (s, 2H), 2.99 - 2.85 (m, 1H), 2.62 - 2.58 (m, 2H), 2.46 - 2.39 (m, 1H), 2.23 - 2.19 (m, 1H), 2.00 - 1.97 (m, 1H).

Compound B24: 3-(1'-((1H-indazol-7-yl)methyl)-3'-hydroxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



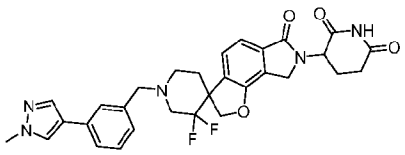
[0524] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between 3-(3'-hydroxy-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B29**) and 1H-indazole-7-carbaldehyde as a white solid. LC-MS (ESI): mass calcd. for $C_{27}H_{27}N_5O_5$, 501.54; m/z found, 502.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 10.98 (s, 1H), 8.15 - 8.10 (m, 1H), 7.70 - 7.60 (m, 4H), 7.10 - 7.06 (m, 1H), 5.11 - 4.17 (m, 6H), 4.07 - 3.48 (m, 3H), 2.95 - 2.57 (m, 4H), 2.46 - 2.40 (m, 1H), 2.24 - 2.18 (m, 1H), 2.04 - 1.95 (m, 2H), 1.74 - 1.57 (m, 2H).

Compound B25: 3-(1'-benzyl-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



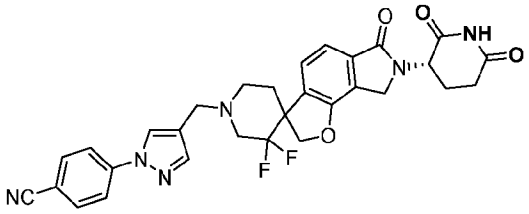
[0525] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between 3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B10**) and benzaldehyde as a white solid. LC-MS (ESI): mass calcd. for $C_{26}H_{25}F_2N_3O_4$, 481.50; m/z found, 482.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (d, J = 3.6 Hz, 1H), 8.17 (s, 1H), 7.50 (d, J = 7.4 Hz, 1H), 7.41 - 7.23 (m, 6H), 5.12 - 5.08 (m, 1H), 4.87 - 4.85 (m, 1H), 4.55 (t, J = 8.0 Hz, 1H), 4.41 (t, J = 16.4 Hz, 1H), 4.24 (t, J = 16.4 Hz, 1H), 3.65 (s, 2H), 3.09 (s, 1H), 2.95 - 2.81 (m, 2H), 2.69 - 2.54 (m, 2H), 2.46 - 2.36 (m, 1H), 2.28 (t, J = 11.2 Hz, 1H), 2.14 (t, J = 11.6 Hz, 1H), 2.04 - 1.88 (m, 2H).

Compound B26: 3-(3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



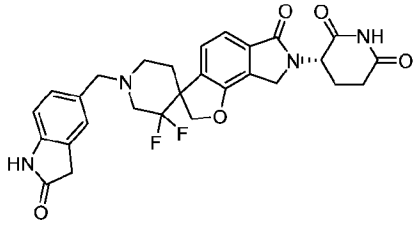
[0526] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between 3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B10**) and 3-(1-methyl-1H-pyrazol-4-yl)benzaldehyde (Intermediate B27) as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{29}F_2N_5O_4$, 561.59; m/z found, 562.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.14 (s, 1H), 7.85 (s, 1H), 7.52 - 7.47 (m, 3H), 7.37 - 7.32 (m, 2H), 7.18 (d, J = 7.6 Hz, 1H), 5.11 - 5.08 (m, 1H), 4.90 - 4.86 (m, 1H), 4.60 - 4.52 (m, 1H), 4.42 (t, J = 16.4 Hz, 1H), 4.25 (t, J = 16.4 Hz, 1H), 3.87 (s, 3H), 3.72 - 3.61 (m, 2H), 3.12 (s, 1H), 2.96 - 2.82 (m, 2H), 2.70 - 2.56 (m, 2H), 2.47 - 2.37 (m, 1H), 2.39 - 2.30 (m, 1H), 2.16 (t, J = 11.6 Hz, 1H), 2.04 - 1.88 (m, 2H).

Compound B27: 4-(4-((7-((S)-2,6-dioxopiperidin-3-yl)-3',3'-difluoro-6-oxo-7,8-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-1'-yl)methyl)-1H-pyrazol-1-yl)benzonitrile



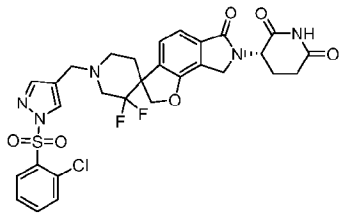
[0527] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 4-(4-formyl-1H-pyrazol-1-yl)benzonitrile (**Intermediate B24**) as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{26}F_2N_6O_4$, 572.20; m/z found, 573.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.63 (s, 1H), 8.07 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H), 7.81 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 5.12 - 5.08 (m, 1H), 4.85 (d, J = 9.4 Hz, 1H), 4.54 (d, J = 9.6 Hz, 1H), 4.43 (d, J = 17.2 Hz, 1H), 4.22 (d, J = 17.2 Hz, 1H), 3.64 (s, 2H), 3.20 - 3.16 (m, 1H), 2.97 - 2.83 (m, 2H), 2.60 - 2.56 (m, 2H), 2.43 - 2.40 (m, 1H), 2.28 (d, J = 13.2 Hz, 1H), 2.13 (t, J = 11.2 Hz, 1H), 1.98 - 1.93 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -107.67 (s), -108.31 (s).

Compound B28: (3S)-3-(3',3'-difluoro-6-oxo-1'-((2-oxoindolin-5-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0528] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 2-oxoindoline-5-carbaldehyde (**Intermediate B25**) as a white solid. LC-MS (ESI): mass calcd. for $C_{28}H_{26}F_2N_4O_5$, 536.19; m/z found, 537.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.37 (s, 1H), 8.49 (s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.18 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 5.11 - 5.07 (m, 1H), 4.88 - 4.83 (m, 1H), 4.56 - 4.54 (m, 1H), 4.41 (t, J = 17.2 Hz, 1H), 4.24 (t, J = 17.2 Hz, 1H), 3.56 (s, 2H), 3.48 (s, 2H), 3.09 (s, 1H), 2.91 - 2.83 (m, 2H), 2.62 - 2.56 (m, 2H), 2.50 - 2.48 (m, 1H), 2.26 - 2.23 (m, 1H), 2.10 - 2.06 (m, 1H), 2.00 - 1.96 (m, 2H).

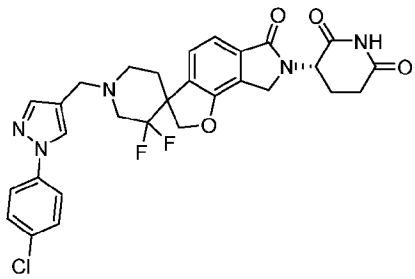
Compound B29: (3S)-3-(1'-((1-((2-chlorophenyl)sulfonyl)-1H-pyrazol-4-yl)methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0529] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1-((2-chlorophenyl)sulfonyl)-1H-pyrazole-4-carbaldehyde (**Intermediate B26**) as a white solid. LC-MS (ESI): mass calcd. for $C_{29}H_{26}ClN_5O_6S$, 645.12; m/z found, 646.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (d, J = 4.0 Hz, 1H), 8.55 (s, 1H), 8.25 - 8.19 (m, 1H), 7.90 (s, 1H), 7.82 (dd, J = 12.2, 4.8 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 5.14 - 5.04 (m, 1H), 4.85 - 4.76 (m, 1H),

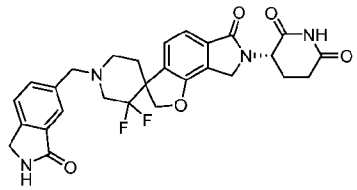
4.53 (s, 1H), 4.42 (t, J = 17.0 Hz, 1H), 4.25 (t, J = 17.0 Hz, 1H), 3.65 (s, 2H), 3.13 (s, 2H), 2.91 - 2.88 (m, 2H), 2.60 (d, J = 15.4 Hz, 1H), 2.44 - 2.40 (m, 1H), 2.28 - 2.25 (m, 1H), 2.13 - 2.11 (m, 1H), 2.01 - 1.86 (m, 2H). ^{19}F NMR (376 MHz, DMSO) δ -107.88 (s), -108.52 (s).

Compound B30: (3S)-3-(1'-((1-(4-chlorophenyl)-1H-pyrazol-4-yl)methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0530] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1-(4-chlorophenyl)-1H-pyrazole-4-carbaldehyde as a white solid. LC-MS (ESI): mass calcd. for $C_{29}H_{26}ClF_2N_5O_4$, 581.16; m/z found, 582.4 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.49 (s, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.73 (s, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.48 - 7.46 (m, 1H), 7.33 (d, J = 7.8 Hz, 1H), 5.13 - 5.08 (m, 1H), 4.85 (t, J = 9.4 Hz, 1H), 4.55 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 17.2 Hz, 1H), 4.24 (t, J = 17.2 Hz, 1H), 3.63 (s, 2H), 3.18 (s, 1H), 2.98 - 2.82 (m, 2H), 2.70 - 2.54 (m, 2H), 2.45 - 2.40 (m, 1H), 2.34 - 2.29 (m, 1H), 2.12 (t, J = 15.2 Hz, 1H), 2.01 - 1.95 (m, 2H).

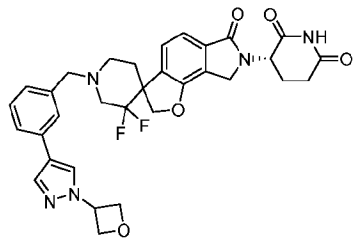
Compound B31: (3S)-3-(3',3'-difluoro-6-oxo-1'-((3-oxoisoindolin-5-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0531] The title compound was prepared according to the procedure described in Compound B1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 3-oxoisoindoline-5-carbaldehyde (**Intermediate B29**) as a white solid. LC-MS (ESI): mass

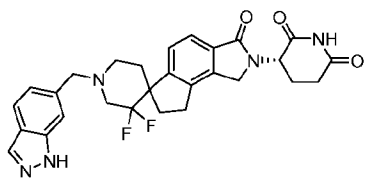
calced for: $C_{28}H_{26}F_2N_4O_5$ 536.54; m/z found, 537.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (d, J = 3.8 Hz, 1H), 8.56 (s, 1H), 7.66 (s, 1H), 7.57 (s, 2H), 7.52 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 5.18 - 5.03 (m, 1H), 4.89 - 4.85 (m, 1H), 4.57 - 4.55 (m, 1H), 4.43 (t, J = 16.8 Hz, 1H), 4.37 (s, 2H), 4.24 (t, J = 16.8 Hz, 1H), 3.77 (s, 2H), 3.13 (s, 1H), 2.98 - 2.80 (m, 2H), 2.66 - 2.57 (m, 2H), 2.45 - 2.36 (m, 1H), 2.35 - 2.26 (m, 1H), 2.18 (s, 1H), 1.99 - 1.90 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -108.01 (s), -108.65 (s).

Compound B32: (3S)-3-(3',3'-difluoro-1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0532] The title compound was prepared according to the procedure described in Compound B1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzaldehyde (**Intermediate B28**) as a white solid. LC-MS (ESI): mass calced for: $C_{32}H_{31}F_2N_5O_5$ 603.63; m/z found, 604.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.03 (s, 1H), 7.53 (dd, J = 15.0, 7.2 Hz, 3H), 7.40 - 7.31 (m, 2H), 7.20 (d, J = 7.6 Hz, 1H), 5.64 - 5.56 (m, 1H), 5.11 - 5.07 (m, 1H), 4.98 - 4.90 (m, 4H), 4.87 (dd, J = 10.0, 5.4 Hz, 1H), 4.56 (t, J = 8.2 Hz, 1H), 4.41 (t, J = 16.6 Hz, 1H), 4.24 (t, J = 16.6 Hz, 1H), 3.67 (s, 2H), 3.14 (s, 1H), 2.88 (d, J = 12.4 Hz, 2H), 2.65 - 2.57 (m, 2H), 2.46 - 2.37 (m, 1H), 2.36 - 2.25 (m, 1H), 2.19 - 2.13 (m, 1H), 2.00 - 1.93 (m, 2H). ^{19}FNMR (376 MHz, DMSO-d_6) δ -107.93 (s), -108.58 (s).

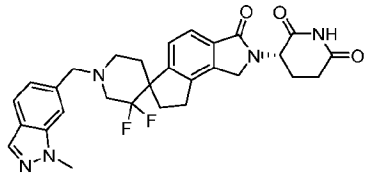
Compound B33: (3S)-3-(1'-((1H-indazol-6-yl)methyl)-3',3'-difluoro-3-oxo-1,3,7,8-tetrahydro-2H-spiro[cyclopenta[e]isoindole-6,4'-piperidin]-2-yl)piperidine-2,6-dione



[0533] The title compound was prepared according to the procedure described in Compound

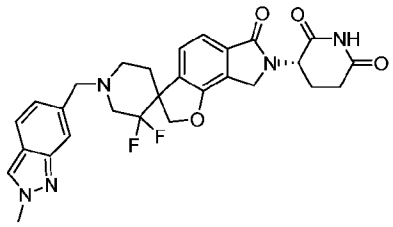
B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1H-indazole-6-carbaldehyde as a white solid. LC-MS (ESI) mass calcd. for $C_{28}H_{27}F_2N_5O_3$, 519.21; m/z found, 520.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.09 (s, 1H), 10.97 (s, 1H), 8.07 (s, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.57 - 7.47 (m, 2H), 7.34 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 5.11 - 5.07 (m, 1H), 4.89 (d, J = 9.8 Hz, 1H), 4.60 - 4.59 (m, 1H), 4.43 (d, J = 17.0 Hz, 1H), 4.23 (d, J = 17.2 Hz, 1H), 3.96 (s, 2H), 3.06 - 2.84 (m, 3H), 2.63 - 2.53 (m, 2H), 2.43 - 2.36 (m, 2H), 2.33 (s, 1H), 2.00 - 1.97 (m, 2H).

Compound B34: (3S)-3-(3',3'-difluoro-1'-((1-methyl-1H-indazol-6-yl)methyl)-3-oxo-1,3,7,8-tetrahydro-2H-spiro[cyclopenta[e]isoindole-6,4'-piperidin]-2-yl)piperidine-2,6-dione



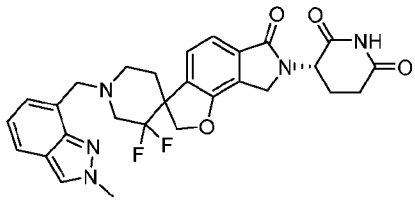
[0534] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1-methyl-1H-indazole-6-carbaldehyde (**Intermediate B30a**) as a white solid. LC-MS (ESI) mass calcd. for $C_{28}H_{27}F_2N_5O_4$, 535.20; m/z found, 536.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.02 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.57 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 5.14 - 5.04 (m, 1H), 4.89 (dd, J = 10.0, 5.2 Hz, 1H), 4.58 - 4.56 (m, 1H), 4.50 - 4.34 (m, 1H), 4.34 - 4.18 (m, 1H), 4.04 (s, 3H), 3.84 (s, 2H), 3.22 - 3.18 (m, 1H), 2.95 - 2.90 (m, 2H), 2.78 - 2.73 (m, 1H), 2.62 - 2.56 (m, 1H), 2.46 - 2.38 (m, 1H), 2.33 - 2.18 (m, 2H), 1.99 - 1.97 (m, 2H).

Compound B35: (3S)-3-(3',3'-difluoro-1'-((2-methyl-2H-indazol-6-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



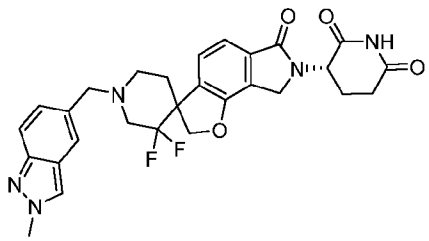
[0535] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 2-methyl-2H-indazole-6-carbaldehyde (**Intermediate B30b**) as a white solid. LC-MS (ESI): mass calcd for: $C_{28}H_{27}F_2N_5O_4$ 535.20; m/z found, 536.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.29 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 10.4 Hz, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 5.11 - 5.07 (m, 1H), 4.86 (d, J = 9.8 Hz, 1H), 4.56 (s, 1H), 4.41 (t, J = 16.8 Hz, 1H), 4.24 (t, J = 16.8 Hz, 1H), 4.15 (s, 3H), 3.71 (d, J = 5.4 Hz, 2H), 3.11 (s, 1H), 2.90 - 2.86 (m, 2H), 2.61 - 2.56 (m, 2H), 2.44 - 2.37 (m, 1H), 2.28 (d, J = 13.4 Hz, 1H), 2.19 (d, J = 12.2 Hz, 1H), 2.00 - 1.937 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -107.93 (s), -108.58 (s).

Compound B36: (3S)-3-(3',3'-difluoro-1'-((2-methyl-2H-indazol-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



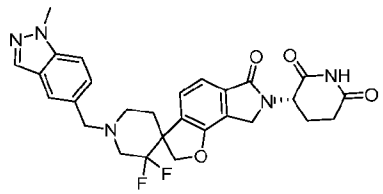
[0536] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 2-methyl-2H-indazole-7-carbaldehyde (**Intermediate B31b**) a white solid. LC-MS (ESI): mass calcd for: $C_{28}H_{27}F_2N_5O_4$ 535.55; m/z found, 536.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.34 (s, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 6.8 Hz, 1H), 7.09 - 6.99 (m, 1H), 5.16 - 5.03 (m, 1H), 4.87 (dd, J = 9.8, 5.6 Hz, 1H), 4.56 (d, J = 8.0 Hz, 1H), 4.41 (t, J = 16.8 Hz, 1H), 4.26 (t, J = 16.8 Hz, 1H), 4.18 (s, 3H), 4.02 (s, 2H), 3.23 (s, 1H), 2.98 - 2.87 (m, 2H), 2.77 - 2.58 (m, 2H), 2.46 - 2.18 (m, 3H), 2.01 - 1.89 (m, 2H). ^{19}F NMR (376 MHz, DMSO) δ -107.95 (s), -108.59 (s).

Compound B37: (3S)-3-(3',3'-difluoro-1'-((2-methyl-2H-indazol-5-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0537] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 2-methyl-2H-indazole-5-carbaldehyde (**Intermediate B32b**) as a white solid. LC-MS (ESI): mass calcd. for $C_{28}H_{27}F_2N_5O_4$, 535.20; m/z found, 536.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.29 (s, 1H), 7.57 (d, J = 10.0 Hz, 2H), 7.50 (d, J = 7.2 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 5.11 - 5.07 (m, 1H), 4.87 - 4.84 (m, 1H), 4.57 - 4.55 (m, 1H), 4.41 (t, J = 16.6 Hz, 1H), 4.24 (t, J = 16.6 Hz, 1H), 4.15 (s, 3H), 3.68 (s, 2H), 3.16 - 3.07 (m, 1H), 2.94 - 2.87 (m, 2H), 2.71 - 2.55 (m,2H), 2.45 - 2.37 (m, 1H), 2.33 - 2.26 (m,1H), 2.21 - 2.10 (m, 1H), 2.04 - 1.91 (m, 2H).

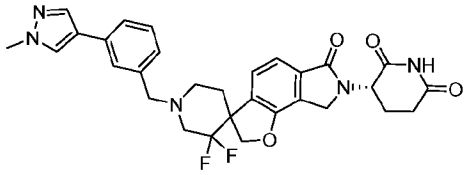
Compound B38: (3S)-3-(3',3'-difluoro-1'-((1-methyl-1H-indazol-5-yl) methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione



[0538] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1-methyl-1H-indazole-5-carbaldehyde (**Intermediate B32a**) as a white solid. LC-MS (ESI): mass calcd. for $C_{28}H_{27}F_2N_5O_4$, 535.20; m/z found, 536.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.02 (s, 1H), 7.67 (s, 1H), 7.61 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 9.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 5.11 - 5.07 (m, 1H), 4.87 (d, J = 9.8 Hz, 1H), 4.55 (s, 1H), 4.46 - 4.35 (m, 1H), 4.28 - 4.19 (m, 1H), 4.04 (s, 3H), 3.75 (s, 2H), 3.13 - 3.07 (m, 1H), 2.90 - 2.85 (m, 2H), 2.62 - 2.56 (m, 2H), 2.42 - 2.35 (m, 1H), 2.29 - 2.27 (m, 1H), 2.18 - 2.15 (m, 1H), 1.99 - 1.92 (m, 2H).

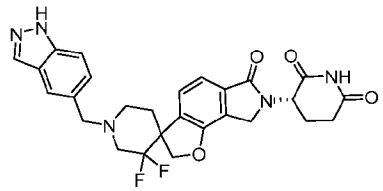
Compound B39: (3S)-3-(3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl) benzyl)-6-oxo-

6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione



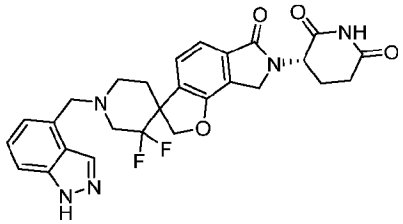
[0539] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 3-(1-methyl-1H-pyrazol-4-yl)benzaldehyde (**Intermediate B27**) as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{29}F_2N_5O_4$, 561.22; m/z found, 562.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (d, J = 4.0 Hz, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.49 (dd, J = 13.6, 7.2 Hz, 3H), 7.37 - 7.31 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 5.12 - 5.08 (m, 1H), 4.87 (dd, J = 9.8, 5.8 Hz, 1H), 4.57 (d, J = 8.4 Hz, 1H), 4.41 (t, J = 16.8 Hz, 1H), 4.24 (t, J = 16.8 Hz, 1H), 3.87 (s, 3H), 3.70 - 3.61 (m, 2H), 3.13 - 3.10 (m, 1H), 2.96 - 2.84 (m, 2H), 2.68 - 2.56 (m, 2H), 2.43 - 2.41 (m, 1H), 2.34 - 2.26 (m, 1H), 2.16 (t, J = 11.8 Hz, 1H), 2.02 - 1.91 (m, 2H).

Compound B40: (3S)-3-(1'-((1H-indazol-5-yl) methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione



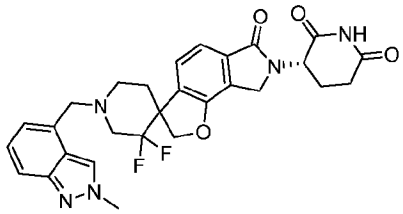
[0540] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1H-indazole-5-carbaldehyde as a white solid. LC-MS (ESI): mass calcd. for $C_{27}H_{25}F_2N_5O_4$, 521.19; m/z found, 522.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 10.97 (s, 1H), 8.05 (s, 1H), 7.68 (s, 1H), 7.54 - 7.48 (m, 2H), 7.35 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 5.11 - 5.07 (m, 1H), 4.86 (dd, J = 9.8, 5.6 Hz, 1H), 4.56 (d, J = 8.8 Hz, 1H), 4.41 (t, J = 16.8 Hz, 1H), 4.24 (t, J = 16.8 Hz, 1H), 3.77 - 3.67 (m, 2H), 3.11 (s, 1H), 2.88 (d, J = 11.6 Hz, 2H), 2.65 - 2.54 (m, 2H), 2.43 - 2.41 (m, 1H), 2.27 (d, J = 11.4 Hz, 1H), 2.15 (t, J = 11.4 Hz, 1H), 1.98 (d, J = 11.8 Hz, 2H).

Compound B41: (3S)-3-(1'-((1H-indazol-4-yl)methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



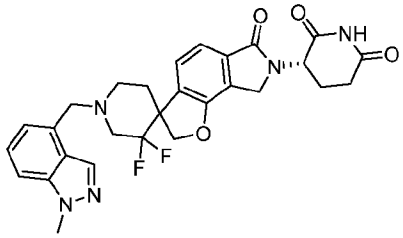
[0541] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1H-indazole-4-carbaldehyde as a yellow solid. LC-MS (ESI): mass calcd. for $C_{27}H_{25}F_2N_5O_4$, 521.19; m/z found, 522.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 10.97 (s, 1H), 8.28 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.34 - 7.28 (m, 2H), 7.06 (d, J = 7.0 Hz, 1H), 5.14 - 5.05 (m, 1H), 4.90 - 4.86 (m, 1H), 4.57 (d, J = 8.2 Hz, 1H), 4.41 (t, J = 16.4 Hz, 1H), 4.24 (t, J = 16.4 Hz, 1H), 3.96 (s, 2H), 3.20 - 3.13 (m, 1H), 2.90 - 2.86 (m, 2H), 2.75 - 2.54 (m, 2H), 2.46 - 2.35 (m, 1H), 2.29 - 2.16 (m, 2H), 2.01 - 1.95 (m, 2H).

Compound B42: (3S)-3-(3',3'-difluoro-1'-((2-methyl-2H-indazol-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



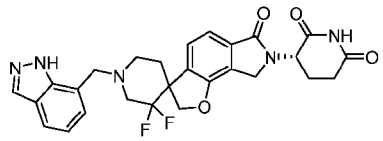
[0542] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 2-methyl-1H-indazole-4-carbaldehyde (**Intermediate B33b**) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{28}H_{27}F_2N_5O_4$, 535.20; m/z found, 536.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.55 - 7.48 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.19 (dd, J = 8.6, 6.8 Hz, 1H), 6.97 (d, J = 6.8 Hz, 1H), 5.15 - 5.05 (m, 1H), 4.88 - 4.85 (m, 1H), 4.58 - 456 (m, 1H), 4.47 - 4.36 (m, 1H), 4.27 - 4.24 (m, 1H), 4.20 (s, 3H), 3.87 (s, 2H), 3.18 - 3.15 (m, 1H), 2.95 - 2.82 (m, 2H), 2.70 (t, J = 10.2 Hz, 1H), 2.62 - 2.56 (m, 1H), 2.49 - 2.40 (m, 1H), 2.31 - 2.15 (m, 2H), 1.99 - 1.95 (m, 2H).

Compound B43: (3S)-3-(3',3'-difluoro-1'-((1-methyl-1H-indazol-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



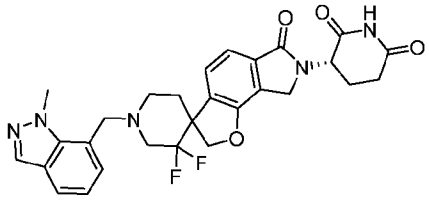
[0543] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1-methyl-1H-indazole-4-carbaldehyde (**Intermediate B33a**) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{28}H_{27}F_2N_5O_4$, 535.20; m/z found, 536.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (d, J = 3.8 Hz, 1H), 8.27 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 6.4 Hz, 1H), 5.17 - 5.03 (m, 1H), 4.93 - 4.85 (m, 1H), 4.53 - 4.50 (m, 1H), 4.46 - 4.36 (m, 1H), 4.27 - 4.20 (m, 1H), 4.06 (s, 3H), 3.53 - 3.49 (m, 2H), 3.36 - 3.15 (m, 2H), 3.03 - 2.79 (m, 3H), 2.62 - 2.56 (m, 1H), 2.46 - 2.38 (m, 1H), 2.32 - 2.29 (m, 1H), 2.00 - 1.97 (m, 2H).

Compound B44. 3-(5-(2-methyl-7-(pyrrolidin-1-ylmethyl)oxazolo[4,5-b]pyridin-5-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione



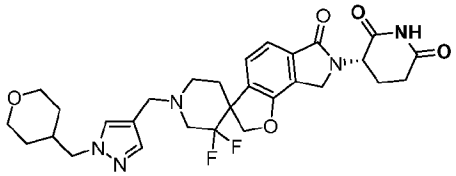
[0544] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1H-indazole-7-carbaldehyde as a white solid. LC-MS (ESI): mass calcd. for $C_{27}H_{25}F_2N_5O_4$, 521.52; m/z found, 522.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H), 10.98 (s, 1H), 8.11 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.15 - 7.05 (m, 1H), 5.14 - 5.04 (m, 1H), 4.88 - 4.85 (m, 1H), 4.57 - 4.45 (m, 1H), 4.41 - 4.36 (m, 1H), 4.28 - 4.20 (m, 1H), 4.00 - 3.87 (m, 2H), 3.22 - 3.17 (m, 1H), 3.01 - 2.84 (m, 2H), 2.72 - 2.55 (m, 2H), 2.46 - 2.17 (m, 3H), 2.02 - 1.87 (m, 2H).

Compound B45: (3S)-3-(3',3'-difluoro-1'-((1-methyl-1H-indazol-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



[0545] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1-methyl-1H-indazole-7-carbaldehyde (**Intermediate B31a**) as a white solid. LC-MS (ESI): mass calcd. for $C_{28}H_{27}F_2N_5O_4$, 535.55; m/z found, 536.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.03 (s, 1H), 7.72 (d, J = 7.4 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 6.8 Hz, 1H), 7.08 - 7.04 (m, 1H), 5.12 - 5.06 (m, 1H), 4.95 - 4.91 (m, 1H), 4.64 - 4.55 (m, 1H), 4.46 - 4.36 (m, 4H), 4.28 - 4.20 (m, 1H), 4.10 - 4.05 (m, 1H), 3.94 - 3.89 (m, 1H), 3.19 - 3.14 (m, 1H), 2.97 - 2.72 (m, 3H), 2.62 - 2.55 (m, 1H), 2.45 - 2.40 (m, 1H), 2.25 - 2.14 (m, 2H), 2.06 - 1.86 (m, 2H).

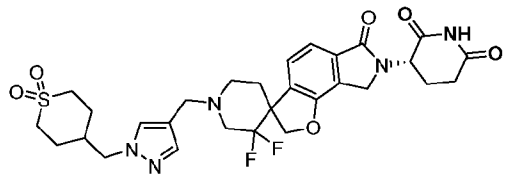
Compound B46: (3S)-3-(3',3'-difluoro-6-oxo-1'-((1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazol-4-yl)methyl)-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0546] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazole-4-carbaldehyde (**Intermediate B17**) as a white solid. LC-MS (ESI): mass calced for: $C_{29}H_{33}F_2N_5O_5$ 569.24; m/z found, 570.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.64 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.37 (s, 1H), 7.31 (d, J = 7.6 Hz, 1H), 5.11 - 5.07 (m, 1H), 4.86 - 4.78 (m, 1H), 4.51 (s, 1H), 4.41 (t, J = 17.0 Hz, 1H), 4.23 (t, J = 17.0 Hz, 1H), 3.97 (d, J = 7.21 Hz, 2H), 3.82 (d, J = 7.6 Hz, 2H), 3.52 (s, 2H), 3.29 - 3.21 (m, 3H), 3.11 (s, 1H), 2.96 - 2.80 (m, 2H), 2.61 - 2.56 (m, 1H), 2.45 - 2.36 (m, 1H), 2.31 - 2.18 (m, 1H), 2.05 - 1.93 (m, 4H), 1.35 (d, J = 11.2 Hz, 2H), 1.28 - 1.15

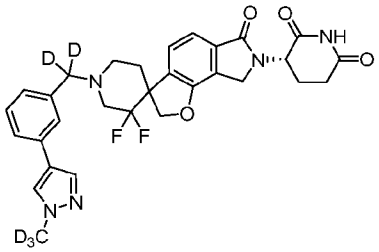
(m, 2H). ^{19}F NMR (376 MHz, DMSO) δ -107.72 (s), -108.36 (s).

Compound B47: (3S)-3-(1'-((1-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl)-1H-pyrazol-4-yl)methyl)-3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0547] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 1-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl)-1H-pyrazole-4-carbaldehyde (**Intermediate B34**) as a white solid. LC-MS (ESI): mass calcd. for $C_{29}H_{33}F_2N_5O_6S$, 617.0; m/z found, 618.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (d, J = 4.4 Hz, 1H), 7.82 (s, 1H), 7.56 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 5.14 - 5.07 (m, 1H), 4.92 (dd, J = 9.8, 5.2 Hz, 1H), 4.63 (s, 1H), 4.45 (t, J = 17.2 Hz, 1H), 4.28 (t, J = 17.2 Hz, 1H), 4.11 (d, J = 7.0 Hz, 4H), 3.65 (s, 1H), 3.26 (s, 2H), 3.14 (dd, J = 19.0, 6.8 Hz, 2H), 3.03 (d, J = 12.6 Hz, 2H), 2.90 (d, J = 11.8 Hz, 1H), 2.71 (s, 1H), 2.60 (d, J = 16.6 Hz, 1H), 2.41 (dd, J = 15.6, 8.4 Hz, 2H), 2.18 (s, 2H), 2.04 - 1.95 (m, 1H), 1.84 (d, J = 12.4 Hz, 2H), 1.70 - 1.64 (m, 2H).

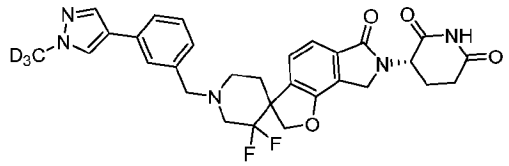
Compound B48: (3S)-3-(3',3'-difluoro-1'-((3-(1-(methyl-d3)-1H-pyrazol-4-yl)phenyl)methyl-d2)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0548] The title compound was prepared according to the procedure described in Compound B-7 by displacement between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 4-(3-(bromomethyl-d2)phenyl)-1-(methyl-d3)-1H-pyrazole (**Intermediate B20**) as a white solid.

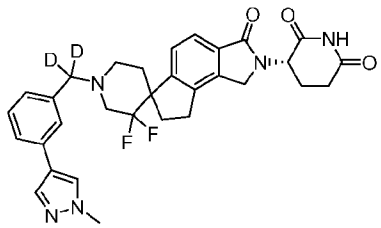
LC-MS (ESI): mass calcd. for $C_{30}H_{24}D_5F_2N_5O_4$, 566.25; m/z found, 567.2 $[M+H]^+$.^{1}H NMR(400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.49 (dd, J = 13.6, 7.2 Hz, 3H), 7.38 - 7.30 (m, 2H), 7.17 (d, J = 7.4 Hz, 1H), 5.11 - 5.06 (m, 1H), 4.87 (d, J = 10.2 Hz, 1H), 4.55 (d, J = 9.2 Hz, 1H), 4.39 (d, J = 17.4 Hz, 1H), 4.26 (d, J = 17.4 Hz, 1H), 3.17 - 3.09 (m, 1H), 2.89 - 2.85 (m, 2H), 2.62 - 2.56 (m, 2H), 2.46 - 2.38 (m, 1H), 2.28 (d, J = 12.8 Hz, 1H), 2.23 - 2.12 (m, 1H), 2.03 - 1.88 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -107.96 (s), -108.60 (s).

Compound B49: (3S)-3-(3',3'-difluoro-1'-(3-(1-(methyl-d3)-1H-pyrazol-4-yl) benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione



[0549] The title compound was prepared according to the procedure described in Compound B-1 by reductive amination between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 3-(1-(methyl-d3)-1H-pyrazol-4-yl)benzaldehyde (**Intermediate B23**) as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{26}D_3F_2N_5O_4$, 564.24; m/z found, 565.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.49 (dd, J = 13.8, 7.0 Hz, 3H), 7.33 (dd, J = 7.6, 3.2 Hz, 2H), 7.17 (d, J = 7.4 Hz, 1H), 5.11 - 5.07 (m, 1H), 4.91 - 4.83 (m, 1H), 4.57 (t, J = 8.4 Hz, 1H), 4.41 (t, J = 16.8 Hz, 1H), 4.24 (t, J = 16.8 Hz, 1H), 3.66 (s, 2H), 3.14 - 3.11 (m, 1H), 2.89 - 2.86 (m, 2H), 2.62 - 2.56 (m, 2H), 2.44 - 2.38 (m, 1H), 2.29 (d, J = 9.6 Hz 1H), 2.16 (t, J = 9.0 Hz, 1H), 2.01 - 1.93 (m, 2H).

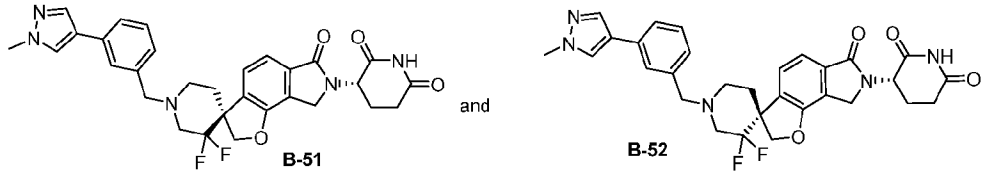
Compound B50: (3S)-3-(3',3'-difluoro-1'-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl-d2)-3-oxo-1,3,7,8-tetrahydro-2H-spiro[cyclopenta[e]isoindole-6,4'-piperidin]-2-yl)piperidine-2,6-dione



[0550] The title compound was prepared according to the procedure described in Compound B-7 by displacement between (3S)-3-(3',3'-difluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (**Intermediate B11**) and 4-(3-(bromomethyl-d2)phenyl)-1-methyl-1H-pyrazole (**Intermediate B22**) as a white solid. LC-MS (ESI): mass calcd. for $C_{30}H_{27}D_2N_5O_4$, 563.60; m/z found, 564.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.13 (s, 1H), 7.85 (s, 1H), 7.49 (dd, J = 13.6, 6.8 Hz, 3H), 7.37 - 7.30 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 5.11 - 5.06 (m, 1H), 4.88 (d, J = 9.8 Hz, 1H), 4.55 (d, J = 8.8 Hz, 1H), 4.47 - 4.34 (m, 1H), 4.31 - 4.18 (m, 1H), 3.87 (s, 3H), 3.14 - 3.12 (m, 1H), 2.89 - 2.85 (m, 2H), 2.68 - 2.57 (m, 2H), 2.43 - 2.25 (m, 2H), 2.16 (t, J = 11.8 Hz, 1H), 2.04 - 1.88 (m, 2H).

Compound B51: (S)-3-((S)-3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl) benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione (PVT-0006571-001)

Compound B52: (S)-3-((R)-3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl) benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0551] (3S)-3-(3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (100 mg, 178 μmol, 1.0 eq) was purified by chiral Prep-HPLC with ChiralPak IH (5 μm, 250 x 21.2 mm), and mobile phase of A for CO_2 and B for ETOH (0.1% NH_3H_2O) 5-99% over 3 h at a flow rate of 40 mL/min to give (S)-3-((S)-3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (9.60 mg, yield 9 %) as a white solid. (e.e.: 42.20%) and (S)-3-((R)-3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (10.0 mg, yield 10.0%) as a white solid. (e.e.:54.64%).

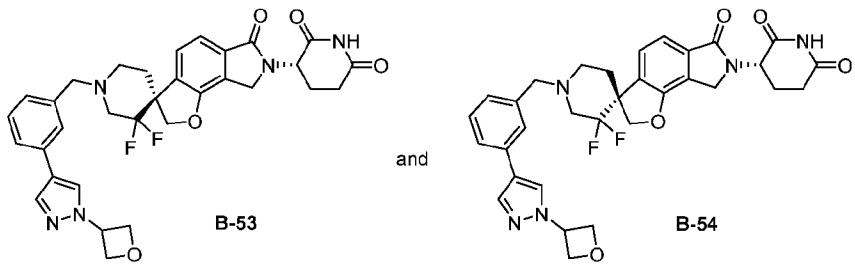
[0552] (S)-3-((S)-3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione: LC-MS (ESI): mass calcd. for $C_{30}H_{29}F_2N_5O_4$, 561.22; m/z found, 562.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.14 (s, 1H), 7.85 (s, 1H), 7.49 (dd, J = 13.8, 7.2 Hz, 3H), 7.37 -

7.31 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 5.11 - 5.06 (m, 1H), 4.87 (dd, J = 9.8, 6.2 Hz, 1H), 4.55 (d, J = 8.8 Hz, 1H), 4.46 - 4.36 (m, 1H), 4.29 - 4.19 (m, 1H), 3.87 (s, 3H), 3.70 - 3.62 (m, 2H), 3.13 (s, 1H), 2.96 - 2.84 (m, 2H), 2.68 - 2.57 (m, 2H), 2.45 - 2.40 (m, 1H), 2.33 - 2.26 (m, 1H), 2.16 (t, J = 11.8 Hz, 1H), 2.01 - 1.91 (m, 2H).

[0553] (S)-3-((R)-3',3'-difluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione: LC-MS (ESI): mass calcd. for $C_{30}H_{29}F_2N_5O_4$, 561.22; m/z found, 562.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.14 (s, 1H), 7.85 (s, 1H), 7.49 (dd, J = 13.8, 7.2 Hz, 3H), 7.36 - 7.30 (m, 2H), 7.17 (d, J = 7.8 Hz, 1H), 5.13 - 5.08 (m, 1H), 4.87 (d, J = 10.0 Hz, 1H), 4.57 (d, J = 9.6 Hz, 1H), 4.41 (t, J = 16.8 Hz, 1H), 4.24 (t, J = 16.8 Hz, 1H), 3.87 (s, 3H), 3.66 (s, 2H), 3.11 (s, 1H), 2.90 - 2.86 (m, 2H), 2.65 - 2.57 (m, 2H), 2.43 - 2.38 (m, 1H), 2.29 (d, J = 11.0 Hz, 1H), 2.16 (t, J = 11.8 Hz, 1H), 2.02 - 1.94 (m, 2H).

Compound B53: (S)-3-((S)-3',3'-difluoro-1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

Compound B54: (S)-3-((R)-3',3'-difluoro-1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



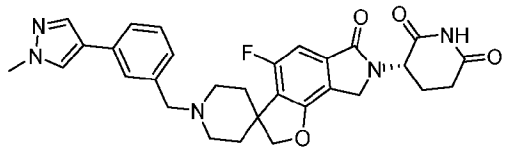
[0554] The racemate product (3S)-3-(3',3'-difluoro-1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (PVT-0006340-001) (400 mg) was separated by SFC Prep-HPLC with Waters Thar 80 preparative SFC (ChiralCel OJ, 5 μm, 250 x 21.2 mm I.D., 5 μm), and mobile phase of A for CO_2 and B for 0.1% 7mol/L NH3 in MeOH over 3 h, at a flow rate of 40 mL/min to give (S)-3-((S)-3',3'-difluoro-1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl) benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione (33.5 mg, yield 8.37 %) as a white solid and (S)-3-((R)-3',3'-difluoro-1'-(3-(1-(oxetan-3-yl)-

1H-pyrazol-4-yl) benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione (59.5 mg, 14.9%) as a white solid.

[0555] (S)-3-((S)-3',3'-difluoro-1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl) benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione (**B-53**): LC-MS (ESI): mass calcd. for $C_{32}H_{31}F_2N_5O_5$, 603.23; m/z found, 604.3[M+H] $^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.38 (s, 1H), 8.14 (s, 1H), 8.03 (s, 1H), 7.58 - 7.48 (m, 3H), 7.35 (dd, J = 20.2, 7.6 Hz, 2H), 7.21 (d, J = 7.6 Hz, 1H), 5.64 - 5.55 (m, 1H), 5.10 - 5.07 (m, 1H), 4.98 - 4.91 (m, 4H), 4.88 (d, J = 10.0 Hz, 1H), 4.56 (d, J = 10.0 Hz, 1H), 4.39 (d, J = 16.8 Hz, 1H), 4.29 - 4.19 (m, 1H), 3.68 (s, 2H), 3.14 (s, 1H), 2.89 (d, J = 12.4 Hz, 2H), 2.62 (t, J = 20.6 Hz, 2H), 2.43 (d, J = 12.0 Hz, 1H), 2.29 (d, J = 11.9 Hz, 1H), 2.13 (d, J = 42.3 Hz, 1H), 1.97 (s, 2H).

[0556] (S)-3-((R)-3',3'-difluoro-1'-(3-(1-(oxetan-3-yl)-1H-pyrazol-4-yl) benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e] isoindole-3,4'-piperidin]-7-yl) piperidine-2,6-dione (**B-54**): LC-MS (ESI): mass calcd. $C_{32}H_{31}F_2N_5O_5$, 603.23; m/z found, 604.3 [M+H] $^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.38 (s, 1H), 8.13 (s, 1H), 8.02 (s, 1H), 7.53 (dd, J = 16.8, 7.6 Hz, 3H), 7.35 (dd, J = 17.8, 8.0 Hz, 2H), 7.20 (d, J = 7.0 Hz, 1H), 5.65 - 5.54 (m, 1H), 5.11- 5.07 (m, 1H), 4.98 - 4.90 (m, 4H), 4.87 (d, J = 9.8 Hz, 1H), 4.57 (d, J = 9.2 Hz, 1H), 4.43 (d, J = 17.6 Hz, 1H), 4.22 (d, J = 16.7 Hz, 1H), 3.67 (s, 2H), 3.12 (s, 1H), 2.91 (t, J = 13.4 Hz, 2H), 2.62 (t, J = 20.6 Hz, 2H), 2.41 (d, J = 13.4 Hz, 1H), 2.35 - 2.25 (m, 1H), 2.18 (d, J = 11.8 Hz, 1H), 1.98 (dd, J = 9.8, 7.1 Hz, 2H).

Example B55: (S)-3-(4-fluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



Step A: tert-butyl (S)-5-amino-4-(4-fluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)-5-oxopentanoate

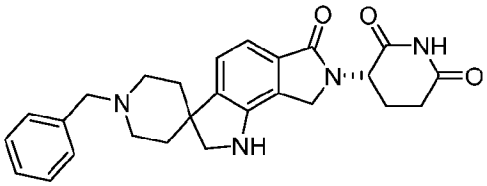
[0557] A solution of tert-butyl (S)-5-amino-4-(4-fluoro-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)-5-oxopentanoate (**Intermediate 36**, 60 mg, 1.0eq.) and 3-(1-methyl-1H-pyrazol-4-yl)benzaldehyde (23 mg, 1.0eq.) in DMAc (3 mL) was added acetic acid (0.01 mL). The resulting reaction mixture was stirred at ambient temperature for 15min.Then sodium triacetoxyborohydride (57mg, 2eq.) was added. The resulting reaction

mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with water (100 mL) and extracted with DCM/MeOH = 10:1 (x3). The organic phases were combined and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The resulting crude material was purified by flash chromatography to afford the title product as a white solid (60 mg). LC-MS (m/z): $[M + H]^+ = 618.40$.

Step B: (S)-3-(4-fluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

[0558] To the suspension of tert-butyl (S)-5-amino-4-(4-fluoro-1'-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)-5-oxopentanoate (60 mg, 1eq) in ACN (1 mL) was added Benzenesulfonic acid (61 mg, 4 eq). The resulting suspension was stirred at 90°C for 5 h. The reaction mixture was allowed to cool to room temperature and added TFA, then purified by prep-HPLC quickly to afford a white solid as the final product (27 mg). LC-MS (m/z): $[M + H]^+ = 544.40$.

Example B56: (S)-3-(1-benzyl-6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)piperidine-2,6-dione



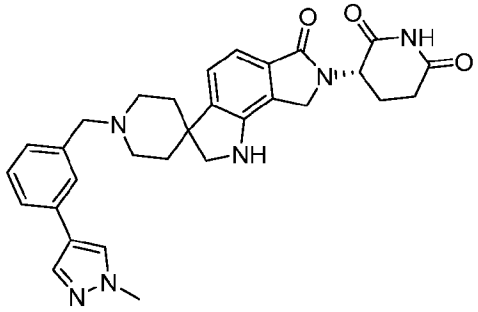
Step A: tert-butyl (S)-5-amino-4-(1-benzyl-6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)-5-oxopentanoate

[0559] A solution of tert-butyl (S)-5-amino-5-oxo-4-(6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)pentanoate (**Intermediate 37**, 15 mg,1.0 eq.) and benzaldehyde (4.50 mg,1.2eq.) in DMAc (3 mL) was added acetic acid (0.01 mL). The resulting reaction mixture was stirred at ambient temperature for 15 min. Then sodium triacetoxyborohydride(15 mg, 2eq.) was added. The resulting reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then diluted with water and extracted with DCM/MeOH =10:1(3X). The organic phases were combined and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The resulting crude material was purified by flash chromatography to afford the title compound (10 mg).

Step B: (S)-3-(1-benzyl-6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)piperidine-2,6-dione

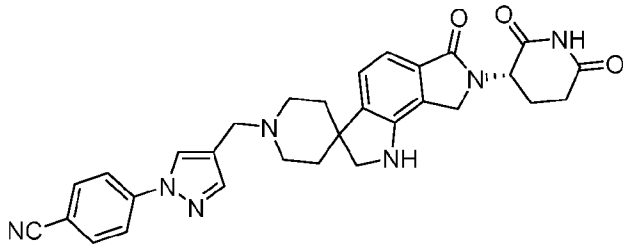
[0560] To the suspension of tert-butyl (S)-5-amino-4-(1-benzyl-6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)-5-oxopentanoate (10 mg,1eq) in CH_3CN (1 mL) was added Benzenesulfonic acid (12 mg,4eq). The resulting suspension was stirred at 90°C for 5 h, The reaction mixture was allowed to cool to room temperature and TFA (50 mg) was added. Then the mixture was purified by prep-HPLC quickly to afford the title compound as a white solid. LC-MS (m/z): $[M + H]^+ = 445.2$.

Example B57: (S)-3-(1-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)piperidine-2,6-dione



[0561] The title compound was prepared according to the procedure described in Compound B-56 by reductive amination between tert-butyl (S)-5-amino-5-oxo-4-(6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)pentanoate (**Intermediate B37**) and 3-(1-methyl-1H-pyrazol-4-yl) benzaldehyde (**Intermediate B27**) followed by acid catalyzed ring cyclization as a white solid. LC-MS (m/z): [M + H]+ = 525.3.

Example B58: (S)-4-(4-((7'-(2,6-dioxopiperidin-3-yl)-6'-oxo-1',6',7',8'-tetrahydro-2'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-1-yl)methyl)-1H-pyrazol-1-yl)benzonitrile



[0562] The title compound was prepared according to the procedure described in Compound B-56 by reductive amination between tert-butyl (S)-5-amino-5-oxo-4-(6'-oxo-1',2',6',8'-tetrahydro-7'H-spiro[piperidine-4,3'-pyrrolo[3,4-g]indol]-7'-yl)pentanoate (**Intermediate B37**) and 4-(4-formyl-1H-pyrazol-1-yl)benzonitrile (Intermediate B24) followed by acid catalyzed ring cyclization as a white solid. LC-MS (m/z): $[M + H]^+ = 536.2$.

III. Biological Assay

For Compound A-1 to A-362

Cereblon Binding Assay

[0563] The binding to cereblon (CRBN) was determined using the Cereblon Binding Kit (Cisbio, #64BDCRBNPEG) following the manufacturer's instruction. Briefly, serially diluted compounds were incubated with GST-tagged wild-type human CRBN protein, XL665-labelled Thalidomide and Europium Cryptate labelled GST antibody at room temperature for about 3 hours. Time Resolved Fluorescence Resonance Energy Transfer (TR-FRET) measurements were acquired on a CALRIOstar plate reader with MARS data analysis software (BMG Labtech), with the following settings: 665/10 nm and 620/10 nm emission, 60 μs delay and 400 μs integration. The TR-FRET ratio was taken as the 665/620 nm intensity ratio. The readings were normalized to the control (0.5%) and the IC_{50} was calculated by nonlinear regression (four parameters sigmoid fitted with variable slope) analysis using the GraphPad Prism 8 software.

Immunoblotting

[0564] Cells were maintained in the appropriate culture medium with 10% FBS at 37°C and an atmosphere of 5% CO^2. All the cell lines were used within three months of thawing fresh vials.

[0565] Cells were lysed 1X Cell Lysis Buffer (Cell Signaling Technology, #9803), resolved by SDS-PAGE NuPAGE gel (Thermo Fisher Scientific), and transferred to a PVDF membrane (Millipore). Membranes were blocked using Odyssey TBS Blocker Buffer (LI-COR). IRDye 680RD and 800CW Dye-labeled secondary antibodies (LI-COR) were used. The washed membranes were scanned using Odyssey CLx imager (LI-COR). The intensity of Western blot signaling was quantitated using the Odyssey software. Primary antibodies used are: Helios (D8W4X) XP® Rabbit mAb (Cell Signaling Technology, #42427) and GAPDH mouse monoclonal antibody (Santa Cruz Biotechnology, sc-47724).

IKZF2 HiBiT assay

[0566] Degradation of IKZF2 protein was determined by IKZF2 HiBiT assay using the Jurkat-IKZF2-HiBiT (Promega) cell line. Briefly, cells were seeded in 384-well flat bottom (Corning #07-201-4423595) at a density of 10,000 cells/well in 20 μl of culture medium. Compounds were serially diluted in culture medium, and 20 μl of the diluted compounds were added to the appropriate wells of the plate. After the addition of compounds, the cells were incubated at 37°C in an atmosphere of 5% CO2 for 24 hours. At the end of treatment, 40 ul of Nano-Glo HiBiT Lytic Detection Reagent (Promega) was added to each well, and then the plates were

incubated at room temperature for 10-20 minutes. The luminescent signal was measured using a CALRIOstar plate reader (BMG Labtech). The readings were normalized to the DMSO-treated cells and the IC_{50} was calculated by nonlinear regression (four parameters sigmoid fitted with variable slope, least squares fit, and no constraint) analysis using the GraphPad Prism 8 software. Results are shown in **Table E2.**

Table E2. Binding activity and degradation potency:

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
Lenalidomide	C	D	D
A1	D	D	D
A2	C	D	D
A3	B	D	C
A4		D	C
A5	C	D	D
A6		D	D
A7		D	D
A8	C	C	C
A9		D	D
A10		D	D
A11	B	D	C
A12	B	D	D
A13		D	D
A14		D	D
A15	C	C	C
A16		D	D
A17		D	C
A18		D	D
A19		D	D
A20		D	D
A21		D	B
A22		D	D

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A23		D	D
A24		D	C
A25		D	C
A26		D	D
A27	C	A	A
A28		D	C
A29	D	D	C
A30		D	D
A31	C	C	B
A32		D	D
A33		D	C
A34		A	B
A35		A	A
A36		B	B
A37		D	C
A38		B	B
A39		A	B
A40		B	B
A41		B	B
A42		D	D
A43		D	C
A44		D	D
A45		C	C
A46		C	C
A47		D	C
A48		D	D
A49	C	A	B
A50		A	B
A51		A	B

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A52	B	A	B
A53		D	C
A54		B	C
A56	C	A	B
A57		B	B
A58		D	C
A59		B	A
A60		D	C
A62		C	C
A64		B	B
A65		D	C
A66		D	C
A67		B	B
A68		D	C
A69	C	A	B
A70		C	B
A71		D	C
A72		D	C
A73		D	C
A74		B	B
A75		B	B
A76		D	D
A77		D	C
A78		C	C
A79		D	D
A80		D	D
A81		D	D
A82		D	D
A83		D	D

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A84		D	C
A85		D	D
A86		D	C
A87	C	A	A
A88		D	D
A89		B	B
A90		D	D
A91		A	B
A92		B	C
A93		B	B
A94		C	C
A95		D	C
A96		B	B
A97		D	C
A98	C	B	B
A99		D	D
A100		D	D
A101		A	B
A102		C	C
A103		C	C
A104		A	A
A105	C	A	B
A106		A	B
A107		A	B
A108		D	C
A109		A	B
A110		A	A
A111		B	B
A112		C	B

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A113		A	B
A114		B	B
A115		B	B
A116	C	A	B
A117		C	C
A118		D	C
A119		A	B
A120		A	B
A121		A	B
A122	C	B	B
A123		D	C
A124	C	C	C
A125	C	A	B
A126	C	C	C
A127	C	A	C
A128	C	B	C
A129	B	A	B
A130	C	A	B
A131	C	B	B
A132	C	A	B
A133	C	A	B
A134	C	A	B
A135		A	B
A136		A	C
A137		A	B
A138		D	C
A139		C	B
A140		D	C
A141		A	B

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A142		B	B
A143		A	B
A144		C	C
A145	B	A	B
A146		A	B
A147		A	B
A148		A	B
A149		D	D
A150		B	B
A151		C	C
A152		B	B
A153		B	B
A154		C	B
A155		D	C
A156		D	D
A157		A	B
A158		D	D
A159		D	C
A160	B	A	B
A161	B	A	B
A162		B	B
A163		A	B
A164		B	B
A165		B	B
A166		B	C
A167		B	C
A168		A	B
A169		A	B
A170	C	A	B

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A171		B	B
A172		A	B
A173		B	B
A174		A	B
A175		D	D
A176		D	C
A177		A	A
A178		A	A
A179		A	A
A180		D	D
A181		C	C
A182		D	C
A183		C	C
A184		D	D
A185		A	B
A186		A	A
A187		C	B
A188		C	B
A189		B	B
A190		D	C
A191		D	D
A192		D	C
A193		D	D
A194		D	D
A195		D	D
A196		B	B
A197		D	D
A198		C	B
A199		D	B

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A200		D	D
A201		D	D
A202		D	D
A203		D	D
A204		D	C
A205		C	C
A206		D	D
A207		D	D
A208		A	B
A209		A	B
A210		D	D
A211		D	D
A212		D	C
A213		A	B
A214		C	C
A215		C	C
A216		B	B
A217		D	D
A218		A	B
A219		C	C
A220		D	D
A221		D	C
A222		D	C
A223		C	C
A224		C	C
A225		D	C
A226		D	C
A227		D	C
A228		D	D

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A229		D	C
A230		D	C
A231		C	B
A232		D	C
A233		C	B
A234		D	D
A235		D	D
A236		D	D
A237		B	B
A238		A	B
A239		A	B
A240		A	B
A241		A	B
A242		A	B
A243		B	B
A244		C	B
A245		C	C
A246		D	D
A247		D	D
A248		D	D
A249		D	D
A250		D	D
A251		D	D
A252		D	D
A253		D	D
A254		D	D
A255		D	D
A256		D	D
A257		D	D

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A258	D		
A259		D	C
A260		D	C
A261		D	D
A262		A	B
A263		A	B
A264		A	B
A265		A	B
A266		A	B
A267		A	B
A268		A	B
A269		B	B
A270		A	B
A271		D	D
A272		B	B
A273		B	B
A274		B	B
A275		D	C
A276		A	C
A277		A	A
A278		A	A
A279		A	B
A280		A	A
A281		A	A
A282		A	B
A283		B	B
A284		A	B
A285		A	B
A286		B	B

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A287		A	B
A288		A	B
A289		A	B
A290		A	B
A291		A	B
A292		A	B
A293		A	B
A294		A	B
A295		A	B
A296		A	B
A297		A	B
A298		B	B
A299		A	B
A300		A	B
A301		A	B
A302		A	B
A303		C	B
A304		D	C
A305		D	C
A306	D		
A307	D		
A308		D	D
A309		D	C
A310		D	D
A311		D	C
A312		D	C
A313		B	B
A314		A	B
A315		B	C

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A316		D	C
A317		C	C
A318		A	B
A319		D	D
A320		D	C
A321		D	D
A322		D	D
A323		D	D
A324		D	C
A325		D	D
A326		D	C
A327		B	B
A328		A	B
A329		B	B
A330		A	B
A331		D	D
A332		D	D
A333		D	C
A334		D	C
A335		D	D
A336		D	C
A337		B	B
A338		D	D
A339		D	C
A340		D	C
A341		D	D
A342		D	D
A343		D	C
A344		D	C

No.	Binding activity IC_{50}	HiBit assay degradation analysis	
		DC_{50}	D_{max}
A345		D	D
A346		A	B
A347		A	B
A348		A	B
A349		A	B
A350		A	B
A351		D	C
A352		C	D
A353		D	C
A354		D	C
A355		C	C
A356		D	C
A357		A	B
A358		D	C
A359		A	B
A360		A	B
A361		D	C
A362		D	C

IC_{50}: "A": <= 0.01 uM; "B": > 0.01 and <=0.1 uM; "C": > 0.1 and <= 1 uM; and "D": >1 uM
DC_{50}: "A": <= 50 nM; "B": >50 and <=200 nM; "C": > 200 and <= 500 nM; and "D" > 500 nM.
Dmax: "A" >=80%; "B">=60% and <80%; "C">=40% and <60%; and "D" <40%

For Compound B-1 to B-58

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

[0567] 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. Results are summarized in **Table E3**.

Table E3. CRBN binding activity

Example	**CRBN Binding activity IC_{50}**
B1	C
B2	D
B3	A
B4	C
B5	B
B7	B
B8	B
B9	A
B10	B
B11	A
B12	B
B13	B
B14	D
B16	B
B17	C
B18	B
B19	D
B20	C
B21	B
B22	B
B23	C
B28	B
B29	A
B30	D
B31	B

Example	CRBN Binding activity IC_{50}
B32	B
B33	B
B34	B
B35	A
B36	B
B37	A
B38	B
B39	B
B40	B
B41	B
B42	B
B43	D
B44	A
B45	B
B48	B
B49	B
B50	B
B51	A
B52	B

A: IC_{50} < 100 nM; B: 100 nM < IC_{50} < 500 nM; C: 500 nM < IC_{50} < 1000 nM; D: 1000 nM < IC_{50} < 5000 nM; E: 5000 nM < IC_{50} < 10000 nM

***In vitro* Assay: IKZF2 FACS assay**

[0568] Jurkat cells (ATCC, Cat # HB-8065) were cultured in RPMI1640 + 10% FBS + 1% P/S. Cells were treated at desired compound concentrations (0.05 to 10 μM) and DMSO as vehicle control for 24 hrs. After 24 hrs of drug treatment cells were washed, fixed (3.7% PFA, and permeabilized with perm buffer (0.3% Triton X-100 in 1% BSA Solution). Subsequently, cells were stained with IKZF2 (1:100, Cell signaling) primary antibody and Alexa 488-labelend anti-rabbit IgG (1:200, Cell Signaling) secondary antibodies in staining buffer (1% BSA in PBS). Cells were images on iQue Flowcytometer and IKZF2 levels were quantified using iQue

software. Data was further analyzed using XLfit using four parameters dose response curve to determine DC_{50} and D_{max}. The half maximal degradation concentration values (DC_{50}) and maximal degradation percentage (D_{max}, %) of IKZF2 are summarized in **Table E4.**

Table E4. IKZF2 degradation activity by FACS

Example	IKZF2 FACS degradation	
	DC_{50}	D_{max}
B14	B	B
B26	A	A
B27	B	C
B32	A	B
B46	A	B
B51	A	A
B53	A	B
B55	A	B

DC_{50}, A: <10 nM; B: >10 nM.
D_{max}, A: >60%; B: 40-60%; C: <40%

***In vitro* Assay: IKZF2 HiBit assay**

[0569] The HiBiT protein tagging system was applied to modified HEK293T Flp-in-HiBiT cells (polyclone) via a CRISPR/Cas9 - mediated insertion of the HiBiT peptide tag (Promega™) to the N-terminus of the IKZF2 gene locus (Neon™ transfection system). Test and reference compounds are diluted from 1 mM at 3 folds for 11 doses. 25 nL of diluted compound is transfered to assay plates (Corning3570) using ECHO550, the final DMSO concentration @ 0.1%. The cells are seeded in 3000/25 mL/well to compound plates. It is then incubated for 6 hrs in TC incubator. The amount of Nano-Glo® HiBiT lytic reagent needed to perform the desired experiments is calculated. The Nano-Glo® HiBiT lytic reagent is brought to room temperature. The LgBiT protein is diluted to 1:100 and the Nano-Glo® HiBiT lytic substrate is diluted to 1:50 into an appropriate volume of room temperature Nano-Glo® HiBiT lytic buffer. 15 mL of the detection reagent (or without LgBiT) is dispensed to corresponding well according to the layout. The plate is then shaked for 10 mins at room temperature. After briefly centrifuge, the plate is read on Envision. At the indicated timepoints, the Nano-Glo® HiBiT lytic detection system (Promega™) was utilized for detecting bioluminescence ofthe HiBiT tag in treated cells: abundance of the tag is proportionate to the level of luminescence. Following normalization to DMSO, dose-response curves were plotted (GraphPad Prism) to determine

the concentration points at which 50% of HiBiT-Helios degradation was achieved by each compound. The extent of degradation (range of luminescence) from the highest to lowest concentration points was calculated to determine the D_{max}. Results of IKZF2 degradation activity are shown in **Table E5**.

Table E5. IKZF2 degradation activity by HiBit

Example	IKZF2 HiBit degradation	
	DC_{50}	D_{max}
B1	B	C
B2	B	B
B3	C	B
B4	B	B
B5	B	B
B6	B	B
B7	B	B
B8	B	B
B9	B	B
B10	B	B
B11	B	A
B12	B	A
B13	B	B
B14	B	A
B15	B	A
B16	B	C
B17	E	E
B18	E	E
B19	D	C
B20	E	D
B21	B	D
B22	C	D
B23	E	E
B24	C	B

Example	IKZF2 HiBit degradation	
	DC_{50}	D_{max}
B25	B	B
B26	B	A
B27	B	B
B28	B	B
B29	A	A
B30	B	B
B31	B	B
B32	A	B
B33	B	B
B34	B	B
B35	B	B
B36	B	B
B37	B	B
B38	B	B
B39	A	B
B40	B	B
B41	B	B
B42	B	B
B43	B	B
B44	B	A
B45	B	A
B46	B	B
B47	C	B
B48	A	B
B49	A	A
B50	B	B
B51	A	B
B52	B	C
B53	A	A

Example	IKZF2 HiBit degradation	
	DC_{50}	D_{max}
B54	B	B
B55	A	A
B56	C	C
B57	C	B
B58	B	C

DC_{50}, A: < 1 nM; B: 1-10 nM; C: 10 -100 nM; D: 100-1000 nM; E: >1000 nM.
D_{max}, A: >80%; B: 60-80%; C: 40-60%; D: 20-40%; E: < 20%.

***In vitro* Assay: IKZF1 HiBit assay**

[0570] The HiBiT protein tagging system was applied to modified Cells: modified HEK293T Flp-in- HiBiT-IKZF1 stable cell line (polyclone) via a CRISPR/Cas9 - mediated insertion of the HiBiT peptide tag (Promega™) to the N-terminus of the IKZF2 gene locus (Neon™ transfection system).

[0571] Test compound from 10 mM and reference compound (CC-92480 from 50 mM and I-57 from 10 mM) are diluted at 3 folds for 11 doses. 25 nL of diluted compound is transferred to assay plates (Corning3571) using ECHO550, the final DMSO concentration @ 0.1%. The cells are seeded in 3000/25 mL/well to compound plates. The plates are incubated for 6 hrs in TC incubator. The amount of Nano-Glo® HiBiT lytic reagent needed to perform the desired experiments is calculated. The Nano-Glo® HiBiT lytic reagent is brought to room temperature. The LgBiT protein is diluted to 1:100 and the Nano-Glo® HiBiT lytic substrate is brought to 1:50 into an appropriate volume of room temperature Nano-Glo® HiBiT lytic buffer. 15 mL of the detection reagent (or without LgBiT) is dispensed to corresponding well according to the layout. The plate is shaked for 10 mins at room temperature. After briefly centrifuging, the plateis read on Envision. At the indicated timepoints, the Nano-Glo® HiBiT lytic detection system (Promega™) was utilized for detecting bioluminescence ofthe HiBiT tag in treated cells: abundance of the tag is proportionate to the level of luminescence. Following normalization to DMSO, dose-response curves were plotted (GraphPad Prism) to determine the concentration points at which 50% of HiBiT- Ikaros degradation was achieved by each compound. The extent of degradation (range of luminescence) from the highest to lowest concentration points was calculated to determine the D_{max}. Results of IKZF1 degradation activity are shown in **Table E6.**

Table E6. IKZF1 degradation activity by HiBit

Example	IKZF1 HiBit degradation	
	DC_{50}	D_{max}
B1	D	B
B2	C	B
B3	E	C
B4	E	C
B5	E	C
B6	E	C
B7	E	C
B8	E	C
B9	E	C
B10	E	C
B11	E	C
B12	E	C
B13	E	C
B14	E	C
B15	E	C
B16	E	C
B17	E	C
B18	E	C
B19	E	C
B20	E	C
B21	E	C
B22	E	C
B23	E	C
B24	E	C
B25	B	B
B26	E	C
B27	E	C
B28	E	C
B29	B	A

Example	IKZF1 HiBit degradation	
	DC_{50}	D_{max}
B30	E	C
B31	E	C
B32	E	C
B33	E	C
B34	E	C
B35	E	C
B36	A	B
B37	E	C
B38	E	C
B39	E	C
B40	E	C
B41	C	B
B42	E	C
B43	E	C
B44	D	B
B45	C	B
B46	E	C
B47	E	C
B48	E	C
B49	E	C
B50	E	C
B51	E	C
B52	E	C
B53	E	C
B54	E	B
B-55	E	C
B-56	E	C
B-57	E	C
B-58	E	C

DC_{50}, A: < 1 nM; B: 1-10 nM; C: 10 -100 nM; D: 100-1000 nM; E: >1,000 nM.
D_{max}, A: >40%; B: 20-40%; C: < 20%.

IKZF2 degradation and evaluation of IL-2 production

[0572] IKZF2 is important for immunosuppressive activity of regulatory T cells (T_{reg} cells), which is linked to interleukin-2 (IL-2) repression. IKZF2 binds to the IL-2 promoter in T_{reg} cells and suppresses transcriptional activation. IKZF2 knockdown suppresses FoxP3 binding to IL-2 promoter and results in higher IL-2 expression upon stimulation. Further, IKZF2 knockout leads to an unstable CD4 Treg phenotype in mice marked by production of effector cytokines and IKZF2 knockout in Tregs suppresses tumor growth. (Baine I. et al., J Immunol 190, 1008–1016 (2013); Nakagawa, H. et al. Proc National Acad Sci 113, 6248–6253 (2016); Yates, K., et al. Proc National Acad Sci 115, 201720447 (2018).

[0573] To measure whether IKZF2 degradation with the compounds of this disclosure impacts IL-2 production, Jurkat cells (ATCC, Cat # HB-8065) are treated with vehicle control (DMSO) or the compound for 16 -24 hrs. After 16 - 24 hrs of treatment cells are stimulated with CD3/CD28 stimulation beads at a 3:1 ratio for 24 hrs. After 24 hrs, supernatants are collected and the concentration of IL-2 is measured using MSD V-PLEX Human IL-2 Kit (Cat#K151QQD, Mesoscale). The compounds of this disclosure are expected to increase IL-2 production, and thereby increase anti-tumor immunity.

IKZF2 degradation in primary human T_{reg} cells

[0574] To measure whether the compounds of this disclosure can induce degradation of IKZF2 in T_{reg} cells, human peripheral bone marrow cells (PBMCs) obtained from healthy donors purchased from Milestone Biological Science and Technology Company are treated with vehicle control (DMSO) or the compound for various time points (3 – 24 hrs). After desired treatment time, the cells are collected and stained with anti-CD3-APC-Cy7 (Clone SP34-2, BD), anti-CD4-FITC (Clone L200, BD), anti-CD45-BV510 (Clone HI30, Biolegend), and anti-CD25-BV421 (Clone BC96, Biolegend) in cell staining buffer (Biolegend, Cat#420201), washed and fixed with FOXP3 fix/perm buffer (Life Technologies, cat. #00-5523-00) followed by intracellular staining with anti-IKZF2-APC (Clone 22F6, BioLegend), anti-Ikaros-PE-Cy7 (Clone 16B5C71, BioLegend), and anti-FOXP3-PE (clone 206D, Biolegend). Samples are acquired on a Thermo Attune NxT flow cytometer (Thermo Fisher Scientific). IKZF2 mean fluorescence intensity (MFI) and IKZF1 MFI are measured in Tregs (CD4+CD25+ FOXP3+)

cells. The compounds of this disclosure are expected to degrade IKZF2 in T_{reg} cells, thereby suppressing the action of T_{reg} cells.

IKZF2 degradation and T_{eff} cell proliferation

[0575] To measure whether the compounds of this disclosure can enhance effector T cell (T_{eff}) proliferation via suppression of T_{reg} cells, T_{reg} cells and T_{eff} cells from matched human donors are co-cultured in the presence of vehicle control (DMSO) or compound. T_{reg} cells are isolated from human peripheral bone marrow cells (PBMCs) obtained from healthy donors purchased from Milestone Biological Science and Technology Company. CD4 enrichment by negative selection followed by CD25 enrichment by positive selection are performed using the human CD4 T cell isolation kit (cat.#130-096-533) and human CD25 microbeads (cat.#130-092-983) from Miltenyi Biotec (Cambridge, MA) according to manufacturer's instructions. Isolated T_{regs} are expanded for 8-14 days in the presence of compound or DMSO, using T_{reg} expander beads (ThermoFisher, cat.#11129D) or T-cell activator beads (ThermoFisher, cat.#11161D) at a 4:1 or 3:1 ratio, respectively, in the presence of 500 U/mL rhIL-2. Expanded T_{reg} cells are dispensed in co-culture with carboxyfluorescein succinimidyl ester (CFSE)-labelled CD3+ T-Cells from the matched donor at various T_{reg}:CD3+ T cell ratios in the presence of T-cell activator beads or soluble anti-CD3 antibody (30 ng/mL, OKT3, Thermofisher cat.# 16-0037-81). After 3-5 days of incubation, proliferation of CD8+ T_{eff} cells is assessed by analyzing CFSE dye dilution in CD8+ T-Cells (anti-CD8-PerCP/Cyanine5.5, clone SK1, Biolegend) using flow cytometry. Analysis is performed using a Thermo Attune NxT flow cytometer (Thermo Fisher Scientific). T_{eff} cells that proliferate during the co-culture are identified as having diluted CFSE and data are plotted as the proportion of CFSE low, proliferated cells in the final culture. The compounds of this disclosure are expected to suppress T_{reg} cells, thereby enhancing T_{eff} cell proliferation.

In vivo pharmacology and efficacy studies

Cynomolgus moneys

[0576] To determine *in vivo* efficacy of the compounds of this disclosure, non naïve cynomolgus monkeys are treated with a single oral dose of vehicle or the compound. Whole blood from the treated monkeys is collected across time (e.g., various timepoints between 0 hr – 96 hrs) and stained with anti-CD3-APC-Cy7 (Clone SP34-2, BD), anti-CD4-FITC (Clone L200, BD), anti-CD45-BV786 (Clone D058-1283, Biolegend), and anti-CD25-APC (Clone BC96, Biolegend) in cell staining buffer (Biolegend, Cat#420201), washed and fixed with

FOXP3 fix/perm buffer (Life Technologies, cat. #00-5523-00) followed by intracellular staining with anti-IKZF2-PE (Clone 22F6, BioLegend) and anti-FOXP3-BV421 (clone 206D, Biolegend). Samples are acquired on a Thermo Attune NxT flow cytometer (Thermo Fisher Scientific). IKZF2 mean fluorescence intensity (MFI) is measured in T_{regs} (CD4+CD25+FOXP3+) cells. The compounds of this disclosure are expected to suppress IKZF2^{+} T_{regs} in cynomolgus monkeys.

Mice

[0577] To determine *in vivo* efficacy of the compounds of this disclosure, CRBN^{I391V} mice are treated with a single oral dose of vehicle or the compound. CRBN^{I391V} mice are used because a single amino acid difference within the CRBN–Immunomodulatory drug (IMiD) binding region renders mouse CRBN resistant to degradation by IMiDs. A change from Ile 391 to Val in mouse CRBN restores IMiD-induced degradation of IKZF3. Fink, E. C. et al. Blood 132, 1535–1544 (2018); Gemechu, Y. et al. P Natl Acad Sci Usa 115, 11802–11807 (2018).

1. **IKZF2 degradation in mice:** Various doses of the vehicle and compound are tested in the mice and analyzed across time (e.g., various timepoints between 0 hr – 12 hrs) and analyzed using western blot assay to measure the percentage of IKZF2 remaining in tissues (e.g., spleen and thymus). Tissue is lysed in RIPA buffer (Cell Signaling, cat#9806) containing Halt^{TM} protease/phosphatase inhibitor cocktail (Thermo, Cat#78440). After assessing protein concentration by BCA assay (Pierce), equal amounts of protein for each sample are loaded into 4–12% Bis-Tris gels (Invitrogen), transferred to nitrocellulose membranes and immunoblotted with antibodies against Helios (Cell Signaling, Cat#4247) and b-Actin (Cell Signaling, Cat#3700). Membranes are developed on an Odyssey detection system (LI-COR Biosciences) after incubation with IRDye800-labeled goat anti-rabbit IgG and IRDye680-labeled goat anti-mouse IgG (LI-COR) secondary antibodies. The compounds of this disclosure are expected to degrade IKZF2 in CRBN^{I391V} mice.
2. **Tumor growth inhibition in mice:** To develop cancer cell line xenografts, CRBN^{I391V} mice are implanted with MC38 cells (ATCC) subcutaneously to induce tumor formation. MC38 cells (e.g., five million) in 50% Matrigel are injected subcutaneously into CRBN^{I391V} mice to induce tumor formation. Mice are treated with vehicle control (e.g., 5% DMSO, 10% solutol, 85% Water) or the compound once tumors reach ~80-400 mm^3, and sacrificed when tumor volume reached 2000 mm^3 or at the end of the study (whichever occurs first). Tumor sizes and animal weights are measured 2-3 times per week. Tumor volume (mm^3) = (length×width^2)/2. Tumor growth inhibition is

calculated using TGI (%) = (1-((T_e-T_0)/(C_e-C_0))) ´ 100, where 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 The compounds of this disclosure are expected to inhibit MC38 tumor growth in $CRBN^{I391V}$ mice.

INCORPORATION BY REFERENCE

[0578] 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

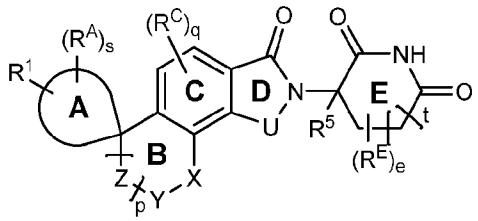
[0579] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth.

[0580] While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I'):



(I'),

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

X is $-C(R^3)_2-$, $-NR^4-$, $-O-$, $-S-$, $-S(=O)-$, or $-S(=O)_2-$;

Y is $-C(R^3)_2-$, $-NR^4-$, $-O-$, $-S-$, $-S(=O)-$, or $-S(=O)_2-$;

each Z is independently $-C(R^3)_2-$, $-NR^4-$, $-O-$, $-S-$, $-S(=O)-$, or $-S(=O)_2-$;

p is 0, 1, or 2;

each R^3 is independently deuterium, 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, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

two geminal R^3 together form oxo; or

two geminal R^3, together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl or 3- to 6-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u;

each R^4 is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u;

Ring A is C_{3-12} carbocycle or 3- to 12-membered heterocycle;

R^1 is hydrogen or $-M-L-Q-R^2$;

M is absent, $-(C=O)-$, $-S(=O)-$, or $-S(=O)_2-$;

L is absent or $[W]_r$;

r is an integer from 1 to 3;

each W is independently $-C(R^L)_2-$, C_{3-4} carbocyclylene, or 3- to 4-membered heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted with one or more R^u;

each R^L is independently hydrogen, deuterium, 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; or

two geminal R^L, together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl or 3- to 6-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u;

Q is absent, -NR^Q-, -O-, -C(=O)-, -S(=O)-, or -$S(=O)_2$-;

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

R^2 is C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^{2a};

each R^{2a} 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, -(C_{1-6} alkylene)-(C_{6-10} aryl), -(C_{1-6} alkylene)-(5- to 10-membered heteroaryl), -(C_{1-6} alkylene)-(C_{3-12} carbocyclyl), -(C_{1-6} alkylene)-(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, alkylene, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u; or

two R^{2a}, together with the atoms to which they are bonded, form C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u;

each occurrence of R^A, R^C, and R^E 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;

q is an integer from 0 to 2;

s is an integer from 0 to 12, as valency permits;

e is an integer selected from 0 to 5;

U is $-CH_2-$ or $-C(=O)-$;

R^5 is hydrogen, deuterium, C_{1-6} haloalkyl, or C_{1-6} alkyl; and

t is an integer from 0 to 2;

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, -(C_{1-6} alkylene)-(C_{6-10} aryl), -(C_{1-6} alkylene)-(5- to 10-membered heteroaryl), -(C_{1-6} alkylene)-(C_{3-12} carbocyclyl), -(C_{1-6} alkylene)-(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, alkylene, 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_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, and 3- to 12-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

R^c and R^d are 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 the heterocyclyl is optionally substituted with one or more R^z,

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

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

2. The compound of claim 1, wherein when p is 0, then X and Y are not both -$C(R^3)_2$; and when p is 1, then X, Y, and Z are not all -$C(R^3)_2$.

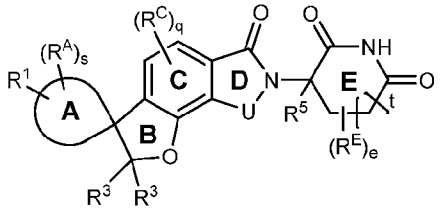
3. The compound of claim 1, wherein X is -O- and Y is -$C(R^3)_2$-.

4. The compound of claim 1, wherein X is -$C(R^3)_2$- and Y is -O-.

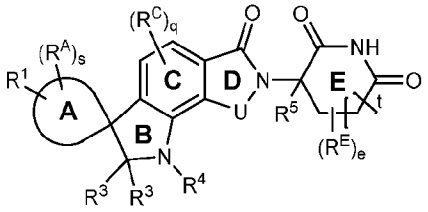
5. The compound of claim 1, wherein X is -NR^4- and Y is -$C(R^3)_2$-.

6. The compound of any one of claims 1-5, wherein p is 0 or 1.

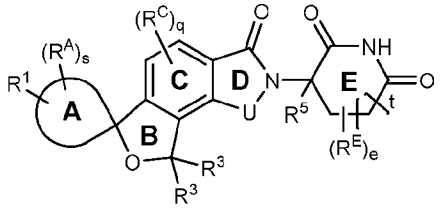
7. The compound of claim 1, wherein the compound is a compound of Formula **(I'-1-ii)**, **(I'-1-iii)**, **(I'-1-iv)**, **(I'-1-v)**, **(I'-1-vi)**, **(I'-1-vii)**, **(I'-1-ix)**, or **(I'-1-xii)**:



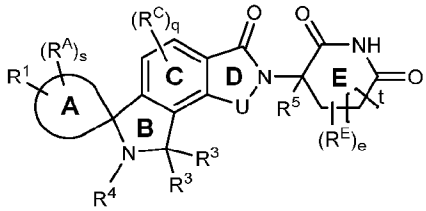
(I'-1-ii),



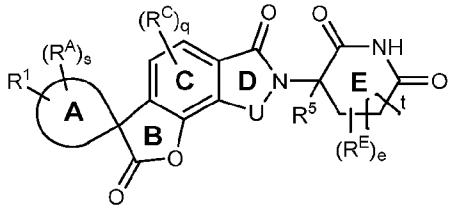
(I'-1-iii),



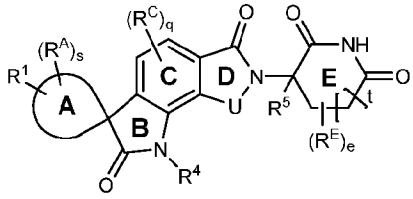
(I'-1-iv),



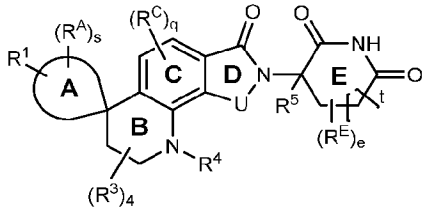
(I'-1-v),



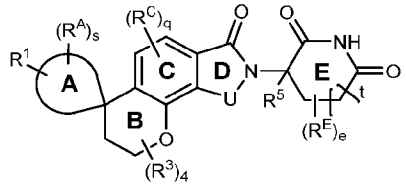
(I'-1-vi),



(I'-1-vii),



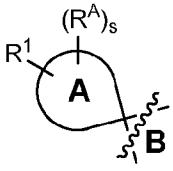
(I'-1-ix), or

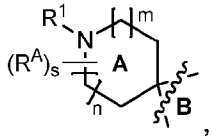


(I'-1-xii),

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

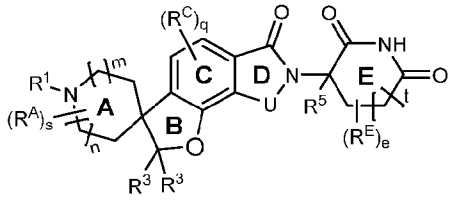
8. The compound of any one of claims 1-7, wherein Ring A is 3- to 12-membered heterocycle.

9. The compound of any one of claims 1-8, wherein  is

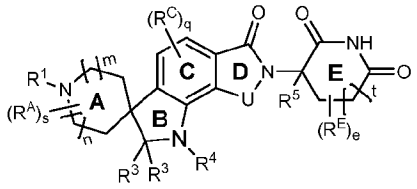


wherein m and n are independently an integer from 0 to 2.

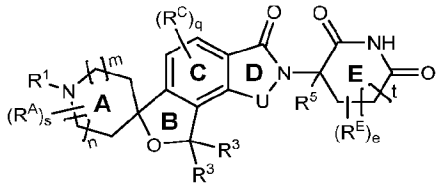
10. The compound of claim 9, wherein the compound is a compound of Formula **(I'-2-ii)**, **(I'-2-iii)**, **(I'-2-iv)**, **(I'-2-v)**, **(I'-2-vi)**, **(I'-2-vii)**, **(I'-2-ix)**, or **(I'-2-xii)**



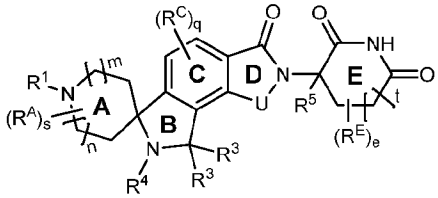
(I'-2-ii),



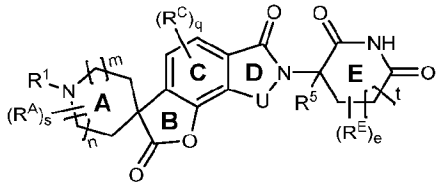
(I'-2-iii),



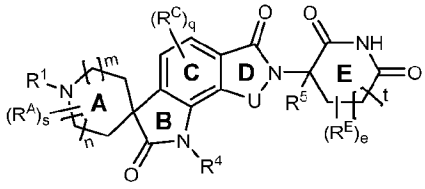
(I'-2-iv),



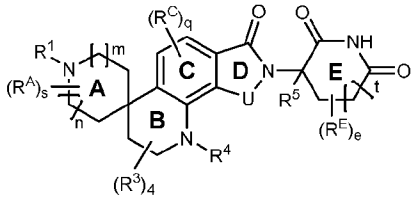
(I'-2-v),



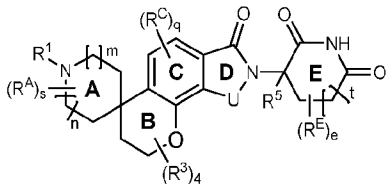
(I'-2-vi),



(I'-2-vii),



(I'-2-ix), or



(I'-2-xii),

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

11. The compound of claim 9 or 10, wherein each of m and n is 1.

12. The compound of any one of claims 1-11, wherein R^1 is hydrogen.

13. The compound of any one of claims 1-11, wherein R^1 is -L-R^2.

14. The compound of claim 13, wherein L is -C(R^L)$_2$-.

15. The compound of claim 14, wherein each R^L is independently hydrogen, deuterium, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

16. The compound of claim 14, wherein each R^L is independently hydrogen, deuterium, or C_{1-6} alkyl.

17. The compound of claim 14, wherein L is $-CH_2-$.

18. The compound of any one of claims 13-17, wherein R^2 is C_{6-10} aryl or 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^{2a}.

19. The compound of claim 18, wherein R^2 is phenyl optionally substituted with one or more R^{2a}.

20. The compound of claim 18, wherein R^2 is 5- to 10-membered heteroaryl optionally substituted with one or more R^{2a}.

21. The compound of claim 18, wherein R^2 is C_{5-10} carbocyclyl optionally substituted with one or more R^{2a}.

22. The compound of claim 18, wherein R^2 is 9- to 10-membered heterocyclyl optionally substituted with one or more R^{2a}.

23. The compound of any one of claims 19-22, wherein each R^{2a} is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

24. The compound of any one of claims 19-22, wherein each R^{2a} is independently oxo, halogen, -CN, -OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkylamino, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -(C_{1-6} alkylene)-(C_{6-10} aryl), -(C_{1-6} alkylene)-(5- to 10-membered heteroaryl), -(C_{1-6} alkylene)-(C_{3-12} carbocyclyl), -(C_{1-6} alkylene)-(3- to 12-membered heterocyclyl), $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^bC(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkylene, alkoxy, alkylamino, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

25. The compound of any one of claims 1-24, wherein each R^3 is independently hydrogen, deuterium, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

26. The compound of any one of claims 1-24, wherein each R^3 is independently hydrogen, deuterium, or C_{1-6} alkyl.

27. The compound of any one of claims 1-26, wherein each R^4 is independently hydrogen or C_{1-6} alkyl.

28. The compound of any one of claims 1-27, wherein each occurrence of R^A, R^C, and R^E is independently oxo, halogen, -CN, $-NO_2$, -OH, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

29. The compound of claim 28, wherein each R^A is independently halogen, -OH, or C_{1-6} alkyl.

30. The compound of claim 28, wherein each R^C is independently halogen, -CN, or C_{1-6} alkyl.

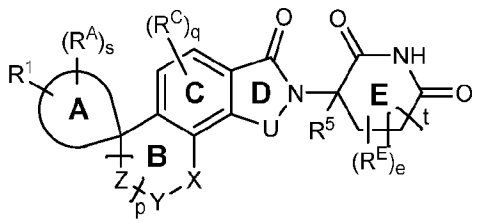
31. The compound of any one of claims 1-30, wherein e is 0.

32. The compound of any one of claims 1-31, wherein U is $-CH_2-$.

33. The compound of any one of claims 1-32, wherein R^5 is hydrogen.

34. The compound of any one of claims 1-33, wherein t is 1.

35. The compound of claim 1, wherein the compound is a compound of Formula (I'):



(I'),

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^1 is hydrogen or -L-R^2;

L is -C(R^L)$_2$-;

each R^L is independently hydrogen, deuterium, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

R^2 is C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^{2a};

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

each occurrence of R^A and R^C is independently oxo, halogen, -CN, -NO_2, -OH, -NH_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

e is 0;

X is -O- or -NR^4-;

each R^4 is independently hydrogen or C_{1-6} alkyl;

Y is -CH_2- or -O-; and

p is 0 or 1.

36. The compound of claim 1, wherein the compound is selected from the compounds in Tables 1 and 2 and pharmaceutically acceptable salts thereof.

37. A pharmaceutical composition comprising the compound of any one of claims 1-36, and a pharmaceutically acceptable excipient.

38. A method of degrading an IKZF2 protein in a subject or biological sample comprising administering the compound of any one of claims 1-36 to the subject or contacting the biological sample with the compound of any one of claims 1-36.

39. Use of the compound of any one of claims 1-36 in the manufacture of a medicament for degrading an IKZF2 protein in a subject or biological sample.

40. A compound of any one of claims 1-36 for use in degrading an IKZF2 protein in a subject or biological sample.

41. A method of treating or preventing a disease or disorder a subject in need thereof, comprising administering to the subject the compound of any one of claims 1-36.

42. Use of the compound of any one of claims 1-36 in the manufacture of a medicament for treating or preventing a disease or disorder in a subject in need thereof.

43. A compound of any one of claims 1-36 for use in treating or preventing a disease or disorder in a subject in need thereof.

44. The method, use, or compound of any one of claims 41-43, wherein the disease or disorder is an IKZF2-mediated disease or disorder.

45. The method, use, or compound of any one of claims 41-43, wherein the disease or disorder is T cell leukemia, T cell lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, myeloid leukemia, non-small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC), nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, carcinoid, or gastrointestinal stromal tumor (GIST).

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/016177

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/20 C07D471/20 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.
A	WO 2022/029573 A1 (NOVARTIS AG [CH]) 10 February 2022 (2022-02-10) claim 1	1-45
A	WO 2021/260528 A1 (NOVARTIS AG [CH]) 30 December 2021 (2021-12-30) claim 1	1-45
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A	WO 2020/165834 A1 (NOVARTIS AG [CH]) 20 August 2020 (2020-08-20) claim 1	1-45

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
12 June 2023	21/06/2023

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

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/016177

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2019/038717 A1 (NOVARTIS AG [CH]; BECKWITH ROHAN ERIC JOHN [US] ET AL.) 28 February 2019 (2019-02-28) claim 1	1-45

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