WEE1 INHIBITORS AND METHODS FOR TREATING CANCER

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6, including U.S. Provisional Application Nos. 63/556,362, filed February 21, 2024, 63/653,067, filed May 29, 2024 and 63/660,402, filed June 14, 2024, each of which is incorporated by reference in their entireties.

BACKGROUND

Field

[0002] The present application relates generally to compounds that are WEE1 inhibitors and/or degraders thereof, and methods of using them to treat conditions characterized by excessive cellular proliferation, such as cancer.

Description

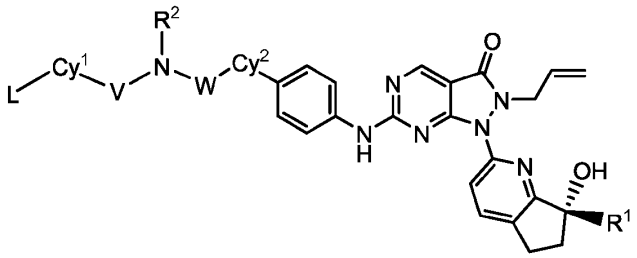
[0003] DNA is constantly damaged from the environment. Light, chemicals, stress, and cellular replication lead to single- or double-stranded breakage along DNA's backbone. Typically, organisms defend against DNA damage by repair proteins that either re-connect, or re-synthesize damaged DNA. The correct functioning of these proteins are essential for life. The incorrect replacement of nucleotides into DNA can cause mutations (and other genetic alterations including but not limited to insertions, deletions, and frameshifts), genetic disease, and loss of protein function. The altogether loss of DNA repair can cause cell death, tumor progression, and cancer.

[0004] Cell cycle checkpoints are important for proper DNA repair, ensuring that cells do not progress with cellular replication until their genomic integrity is restored. WEE1 is a nuclear kinase involved in the G2–M cell-cycle checkpoint arrest for DNA repair before mitotic entry. Normal cells repair damaged DNA during G1 arrest. Cancer cells often have a deficient G1–S checkpoint and depend on a functional G2–M checkpoint for DNA repair. WEE1 is overexpressed in various cancer types.

[0005] Various inhibitors and/or degraders of WEE1 are known to those skilled in the art. *See*, *e.g.*, International Patent Application Publication Nos. WO2019/173082 and WO2020/069105. However, there remains an urgent need for inhibitors and/or degraders of WEE1 that are useful for the treatment of conditions characterized by excessive cellular proliferation, such as cancer.

SUMMARY

[0006] Various embodiments provide a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein the variables **Cy^1**, **Cy^2**, **V**, **W**, **R^1**, **R^2**, **x**, **y**, **z**, **L**, **R^3** and **n** are as defined herein.

[0007] Another embodiment provides a compound, or a pharmaceutically acceptable salt thereof, wherein the compound has a structure selected from those of Compound Nos. 1 to 36 as described herein.

[0008] Another embodiment provides a pharmaceutical composition comprising an effective amount of a compound of Formula (I) or Formula (I') as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0009] Another embodiment provides a method of ameliorating or treating a cancer in a subject comprising administering to the subject an effective amount of a compound of Formula (I) or Formula (I') as described herein, or a compound selected from Compound Nos. 1 to 36 as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, wherein the cancer is selected from a brain cancer, a cervicocerebral cancer, an esophageal cancer, a thyroid cancer, a small cell cancer, a non-small cell cancer, a breast cancer, a lung cancer, a stomach cancer, a gallbladder/bile duct

cancer, a liver cancer, a pancreatic cancer, a colon cancer, a rectal cancer, an ovarian cancer, a choriocarcinoma, an uterus body cancer, an uterocervical cancer, a renal pelvis/ureter cancer, a bladder cancer, a prostate cancer, a penis cancer, a testicular cancer, a fetal cancer, Wilms' cancer, a skin cancer, malignant melanoma, a neuroblastoma, an osteosarcoma, an Ewing's tumor, a soft part sarcoma, an acute leukemia, a chronic lymphatic leukemia, a chronic myelocytic leukemia, polycythemia vera, a malignant lymphoma, multiple myeloma, a Hodgkin's lymphoma and a non-Hodgkin's lymphoma.

[0010] Another embodiment provides a method of inhibiting replication of a malignant growth or a tumor in a subject comprising administering to the subject an effective amount of a compound of Formula (I) or Formula (I') as described herein, or a compound selected from Compound Nos. 1 to 36 as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, wherein the malignant growth or tumor is due to a cancer selected from the list of cancers described above.

[0011] Another embodiment provides a method of ameliorating or treating a malignant growth or a tumor in a subject comprising administering to the subject an effective amount of a compound of Formula (I) as described herein, or a compound selected from Compound Nos. 1 to 36 as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, wherein the malignant growth or tumor is due to a cancer selected from the list of cancers described above.

DETAILED DESCRIPTION

[0012] WEE1 is a tyrosine kinase that is a critical component of the ATR-mediated G2 cell cycle checkpoint control that prevents entry into mitosis in response to cellular DNA damage. ATR phosphorylates and activates CHK1, which in turn activates WEE1, leading to the selective phosphorylation of cyclin-dependent kinase 1 (CDK1) at Tyr15, thereby stabilizing the CDK1-cyclin B complex and halting cell-cycle progression. This process confers a survival advantage by allowing tumor cells time to repair damaged DNA prior to entering mitosis. Inhibition of WEE1 abrogates the G2 checkpoint, promoting cancer cells with DNA damage to enter into unscheduled mitosis and undergo cell death via mitotic catastrophe. Therefore, WEE1 inhibition and/or degradation has the potential to sensitize tumors to DNA-damaging agents, such as cisplatin, and to induce tumor cell death.

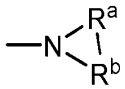
Definitions

[0013] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0014] Whenever a group is described as being "substituted or unsubstituted" or "a substituted or an unsubstituted," that group may be unsubstituted or substituted with one or more of the indicated substituents. If no substituents are indicated, it is meant that the group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), cycloalkyl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, nitro, sulfenyl, sulfinyl, sulfonyl, haloalkyl, hydroxyalkyl, haloalkoxy, an amino, a mono-substituted amine group, a di-substituted amine group and an amine(C_1-C_6 alkyl).

[0015] As used herein, "C_a to C_b" in which "a" and "b" are integers refer to the number of carbon atoms in a group. The indicated group can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-. If no "a" and "b" are designated, the broadest range described in these definitions is to be assumed.

[0016] If two "R" groups are described as being "taken together" the R groups and the atoms they are attached to can form a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R^a and R^b of an NR^aR^b group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



[0017] As used herein, the term "alkyl" refers to a fully saturated aliphatic hydrocarbon group. The alkyl moiety may be branched or straight chain. Examples of

branched alkyl groups include, but are not limited to, iso-propyl, sec-butyl, t-butyl and the like. Examples of straight chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl and the like. The alkyl group may have 1 to 30 carbon atoms (whenever it appears herein, a numerical range such as "1 to 30" refers to each integer in the given range; *e.g.*, "1 to 30 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 30 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 12 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. An alkyl group may be substituted or unsubstituted.

[0018] The term "alkenyl" used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon double bond(s) including, but not limited to, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like. An alkenyl group may be unsubstituted or substituted.

[0019] The term "alkynyl" used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon triple bond(s) including, but not limited to, 1-propynyl, 1-butynyl, 2-butynyl and the like. An alkynyl group may be unsubstituted or substituted.

[0020] As used herein, "cycloalkyl" refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion. As used herein, the term "fused" refers to two rings which have two atoms and one bond in common. As used herein, the term "bridged cycloalkyl" refers to compounds wherein the cycloalkyl contains a linkage of one or more atoms connecting non-adjacent atoms. As used herein, the term "spiro" refers to two rings which have one atom in common and the two rings are not linked by a bridge. Cycloalkyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Examples of mono-cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Examples of fused cycloalkyl groups are decahydronaphthalenyl, dodecahydro-1H-phenalenyl and tetradecahydroanthracenyl;

examples of bridged cycloalkyl groups are bicyclo[1.1.1]pentyl, adamantanyl and norbornanyl; and examples of spiro cycloalkyl groups include spiro[3.3]heptane and spiro[4.5]decane.

[0021] As used herein, "cycloalkenyl" refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be "aryl," as defined herein). Cycloalkenyl groups can contain 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). When composed of two or more rings, the rings may be connected together in a fused, bridged or spiro fashion. A cycloalkenyl group may be unsubstituted or substituted.

[0022] As used herein, "carbocyclyl" refers to a non-aromatic a mono- or multi-cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion, as described herein. Carbocyclyl groups can contain 3 to 30 atoms in the ring(s), 3 to 20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). A carbocyclyl group may be unsubstituted or substituted. Examples of carbocyclyl groups include, but are in no way limited to, cycloalkyl groups and cycloalkenyl groups, as defined herein, and the non-aromatic portions of 1,2,3,4-tetrahydronaphthalene, 2,3-dihydro-1H-indene, 5,6,7,8-tetrahydroquinoline and 6,7-dihydro-5H-cyclopenta[b]pyridine.

[0023] As used herein, "aryl" refers to a carbocyclic (all carbon) monocyclic or multicyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C_6-C_{14} aryl group, a C_6-C_{10} aryl group or a C_6 aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0024] As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more heteroatoms (for example, 1, 2 or 3 heteroatoms), that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s)

of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 16 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s), such as nine carbon atoms and one heteroatom; eight carbon atoms and two heteroatoms; seven carbon atoms and three heteroatoms; eight carbon atoms and one heteroatom; seven carbon atoms and two heteroatoms; six carbon atoms and three heteroatoms; five carbon atoms and four heteroatoms; five carbon atoms and one heteroatom; four carbon atoms and two heteroatoms; three carbon atoms and three heteroatoms; four carbon atoms and one heteroatom; three carbon atoms and two heteroatoms; or two carbon atoms and three heteroatoms. Furthermore, the term "heteroaryl" includes fused ring systems where two rings, such as at least one aryl ring and at least one heteroaryl ring or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline and triazine. A heteroaryl group may be substituted or unsubstituted.

[0025] As used herein, "heterocyclyl" refers to three-, four-, five-, six-, seven-, eight-, nine-, ten-, up to 18-membered monocyclic, bicyclic and tricyclic fully saturated ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle as defined herein may not contain one or more unsaturated bonds. The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion. As used herein, the term "fused" refers to two rings which have two atoms and one bond in common. As used herein, the term "bridged heterocyclyl" refers to compounds wherein the heterocyclyl contains a linkage of one or more atoms connecting non-adjacent atoms. As used herein, the term "spiro" refers to two rings which have one atom in common and the two rings are not linked by a bridge. Heterocyclyl groups can contain 3 to 30 atoms in the ring(s), 3 to

20 atoms in the ring(s), 3 to 10 atoms in the ring(s), 3 to 8 atoms in the ring(s) or 3 to 6 atoms in the ring(s). For example, five carbon atoms and one heteroatom; four carbon atoms and two heteroatoms; three carbon atoms and three heteroatoms; four carbon atoms and one heteroatom; three carbon atoms and two heteroatoms; two carbon atoms and three heteroatoms; one carbon atom and four heteroatoms; three carbon atoms and one heteroatom; or two carbon atoms and one heteroatom. Additionally, any nitrogens in a heterocyclyl may be quaternized. Heterocyclyl groups may be unsubstituted or substituted. Examples of such "heterocyclyl" groups include but are not limited to, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,3-oxathiolane, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazolidine, isoxazolidine, oxazolidine, oxazolidinone, thiazolidine, morpholine, oxirane, piperidine N-Oxide, piperidine, piperazine, pyrrolidine, azepane, pyrrolidone, pyrrolidione, 4-piperidone, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, tetrahydrothiopyran, thiamorpholine and thiamorpholine sulfoxide, thiamorpholine sulfone. Examples of spiro heterocyclyl groups include 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 2-oxa-6-azaspiro[3.3]heptane, 2,6-diazaspiro[3.3]heptane, 2-oxaspiro[3.4]octane and 2-azaspiro[3.4]octane.

[0026] As used herein, "alkylene groups" are straight-chained alkyl groups that are $-CH_2-$ tethering, forming bonds to connect molecular fragments via their terminal carbon atoms. Embodiments of alkylene groups may be represented herein by $-(CH_2)_n-$ where n is an integer in the range of 1 to 30. "Lower" alkylene groups are alkylene groups that contain 1 to 6 carbon atoms. Examples of lower alkylene groups include but are not limited to methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$) and butylene ($-CH_2CH_2CH_2CH_2-$). An alkylene group can be substituted by replacing one or more hydrogen of the alkylene group and/or by substituting both hydrogens on the same carbon with a cycloalkyl group (e.g., ).

[0027] As used herein, the term "hydroxy" refers to a –OH group.

[0028] As used herein, "alkoxy" refers to the Formula –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl) is defined herein. A

non-limiting list of alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (iso-propoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzoxy. An alkoxy may be substituted or unsubstituted.

[0029] As used herein, "acyl" refers to a hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) and heterocyclyl(alkyl) connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl and acryl. An acyl may be substituted or unsubstituted.

[0030] A "cyano" group refers to a "-CN" group.

[0031] The term "halogen atom" or "halogen" as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as, fluorine, chlorine, bromine and iodine.

[0032] A "thiocarbonyl" group refers to a "-C(=S)R" group in which R can be the same as defined with respect to O-carboxy. A thiocarbonyl may be substituted or unsubstituted.

[0033] An "O-carbamyl" group refers to a "-OC(=O)N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-carbamyl may be substituted or unsubstituted.

[0034] An "N-carbamyl" group refers to an "ROC(=O)N(R_A)-" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-carbamyl may be substituted or unsubstituted.

[0035] An "O-thiocarbamyl" group refers to a "-OC(=S)-N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-thiocarbamyl may be substituted or unsubstituted.

[0036] An "N-thiocarbamyl" group refers to an "ROC(=S)N(R_A)-" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-thiocarbamyl may be substituted or unsubstituted.

[0037] A "C-amido" group refers to a "-C(=O)N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A C-amido may be substituted or unsubstituted.

[0038] An "N-amido" group refers to a "RC(=O)N(R_A)-" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-amido may be substituted or unsubstituted.

[0039] An "S-sulfonamido" group refers to a "-SO_2N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.

[0040] An "N-sulfonamido" group refers to a "RSO_2N(R_A)-" group in which R and R_A can be independently hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-sulfonamido may be substituted or unsubstituted.

[0041] An "O-carboxy" group refers to a "RC(=O)O-" group in which R can be hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. An O-carboxy may be substituted or unsubstituted.

[0042] The terms "ester" and "C-carboxy" refer to a "-C(=O)OR" group in which R can be the same as defined with respect to O-carboxy. An ester and C-carboxy may be substituted or unsubstituted.

[0043] A "nitro" group refers to an "–NO_2" group.

[0044] A "sulfenyl" group refers to an "-SR" group in which R can be hydrogen, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A sulfenyl may be substituted or unsubstituted.

[0045] A "sulfinyl" group refers to an "-S(=O)-R" group in which R can be the same as defined with respect to sulfenyl. A sulfinyl may be substituted or unsubstituted.

[0046] A "sulfonyl" group refers to an "SO_2R" group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0047] As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl, tri-haloalkyl and polyhaloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl, 2-fluoroisobutyl and pentafluoroethyl. A haloalkyl may be substituted or unsubstituted.

[0048] As used herein, "haloalkoxy" refers to an alkoxy group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di-haloalkoxy and tri-haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy and 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[0049] The term "amino" as used herein refers to a $-NH_2$ group.

[0050] A "mono-substituted amine" group refers to a "$-NHR_A$" group in which R_A can be an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. The R_A may be substituted or unsubstituted. Examples of mono-substituted amino groups include, but are not limited to, –NH(methyl), –NH(phenyl) and the like.

[0051] A "di-substituted amine" group refers to a "$-NR_AR_B$" group in which R_A and R_B can be independently an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. R_A and R_B can independently be substituted or unsubstituted. Examples of di-substituted amino groups include, but are not limited to, $-N(methyl)_2$, –N(phenyl)(methyl), –N(ethyl)(methyl) and the like.

[0052] As used herein, "amine(alkyl)" group refers to an -(alkylene)-NR'R" radical where R' and R" are independently hydrogen or alkyl as defined herein. An amine(alkyl) may be substituted or unsubstituted. Examples of amine(alkyl) groups include, but are not limited to, $-CH_2NH(methyl)$, $-CH_2NH(phenyl)$, $-CH_2CH_2NH(methyl)$, $-CH_2CH_2NH(phenyl)$, $-CH_2N(methyl)_2$, $-CH_2N(phenyl)(methyl)$, $-NCH_2(ethyl)(methyl)$, $-CH_2CH_2N(methyl)_2$, $-CH_2CH_2N(phenyl)(methyl)$, $-NCH_2CH_2(ethyl)(methyl)$ and the like.

[0053] Where the number of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens. As another example, "C_1-C_3 alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0054] As used herein, a radical indicates species with a single, unpaired electron such that the species containing the radical can be covalently bonded to another species. Hence, in this context, a radical is not necessarily a free radical. Rather, a radical indicates a specific portion of a larger molecule. The term "radical" can be used interchangeably with the term "group."

[0055] The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), a sulfuric acid, a nitric acid and a phosphoric acid (such as 2,3-dihydroxypropyl dihydrogen phosphate). Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, trifluoroacetic, benzoic, salicylic, 2-oxopentanedioic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium, a potassium or a lithium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of a carbonate, a salt of a bicarbonate, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine and salts with amino acids such as arginine and lysine. For compounds of Formula (I) or Formula (I'), those skilled in the art understand that when a salt is formed by protonation of a nitrogen-based group (for example, NH_2), the nitrogen-based group can be associated with a positive charge (for example, NH_2 can become NH_3^+) and the positive charge can be balanced by a negatively charged counterion (such as Cl^-).

[0056] The terms "WEE1 inhibition", "WEE1 inhibitor" and similar terms as used herein refer to inhibiting the activity or function of a WEE1 tyrosine kinase, e.g., by degrading WEE1 tyrosine kinase and/or by reducing the activity of WEE1 tyrosine kinase with regard to mediating phosphorylation of CDK1. A WEE1 inhibitor that functions by degrading WEE1 tyrosine kinase may be referred to herein as a WEE1 degrader.

[0057] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched or a stereoisomeric mixture. In addition, it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

[0058] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

[0059] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0060] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates and hydrates. In some embodiments, the compounds described herein exist in

solvated forms with pharmaceutically acceptable solvents such as water, ethanol or the like. In other embodiments, the compounds described herein exist in unsolvated form. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol or the like. Hydrates are formed when the solvent is water or alcoholates are formed when the solvent is alcohol. 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.

[0061] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

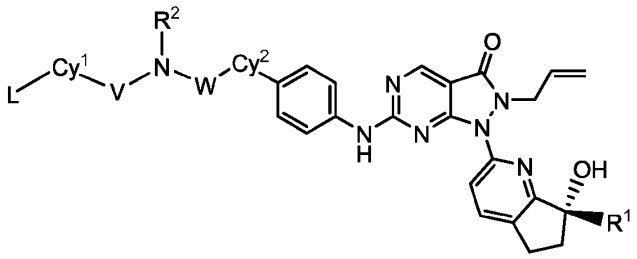
[0062] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; and use of terms like 'preferably,' 'preferred,' 'desired,' or 'desirable,' and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment. In addition, the term "comprising" is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a compound, composition or device, the term "comprising" means that the compound, composition or device includes at least the recited features or components, but may also include additional features or components.

[0063] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from

the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article "a" or "an" does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

Compounds

[0064] This disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein:

Cy¹ and **Cy²** are each independently a substituted or an unsubstituted 4- to 11-membered heterocyclyl;

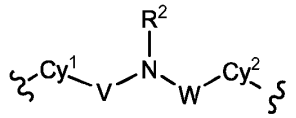
V and **W** are each independently absent or $-CH_2-$;

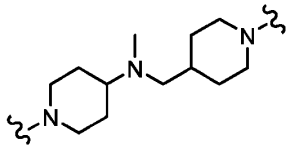
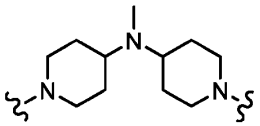
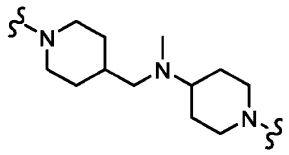
R¹ is a substituted or an unsubstituted C_1-C_6 alkyl;

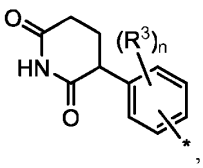
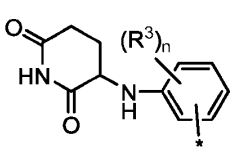
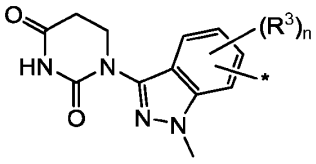
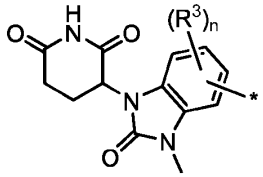
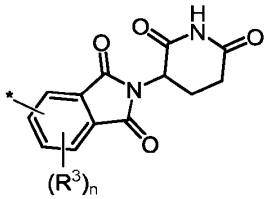
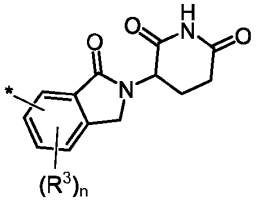
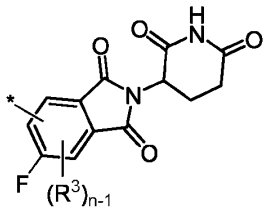
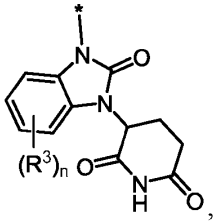
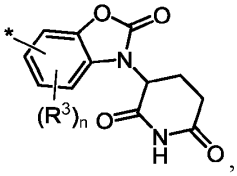
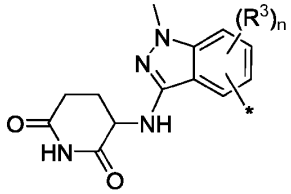
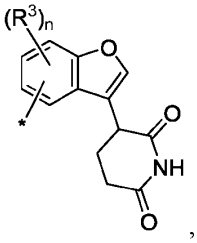
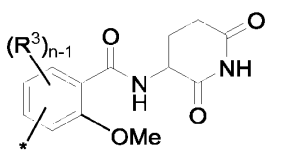
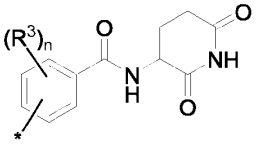
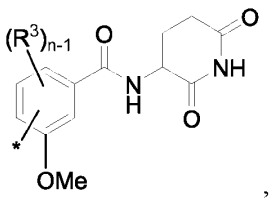
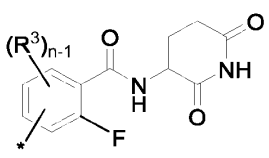
R² is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-C_xH_yD_z$; wherein:

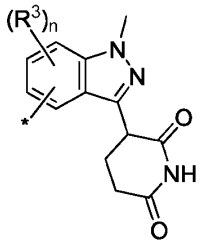
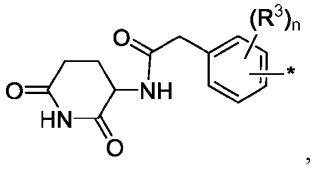
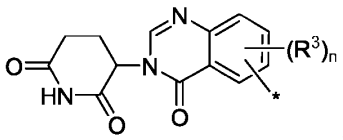
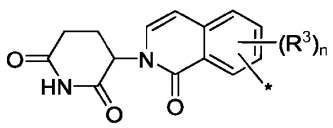
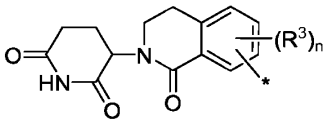
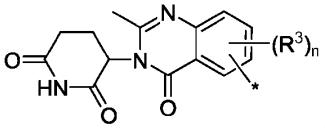
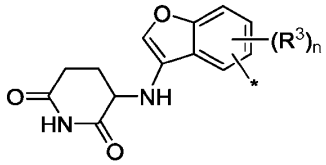
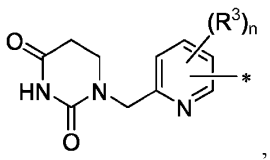
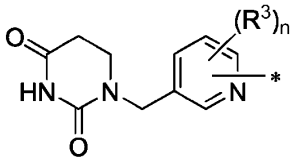
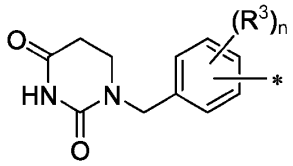
x is an integer selected from 1, 2, 3 and 4;

y is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7 and 8; and

z is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8 and 9; provided that the sum of **y** and **z** is 2**x** + 1 and with the proviso that  is

not ,  or ;

L is , , , , , , , , , , , , , , , , .

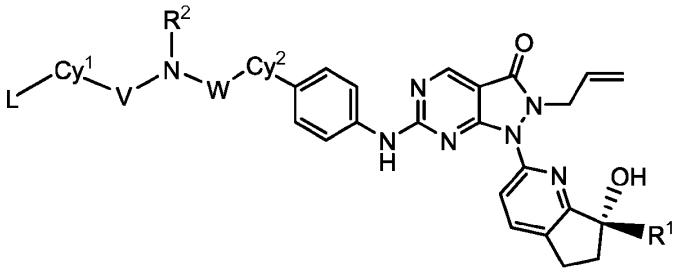

,

,

,

,

,

,

,

,

or

; wherein:

* indicates the point of attachment to **Cy^1**;

R^3 is halogen, C$_1$-C$_4$ alkyl, C$_1$-C$_4$ haloalkyl or C$_1$-C$_4$ alkoxy; and

n is 0, 1 or 2.

[0065] This disclosure relates to a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, having the structure:



(I')

wherein:

Cy^1 and **Cy^2** are each independently a substituted or an unsubstituted 4- to 11-membered heterocyclyl;

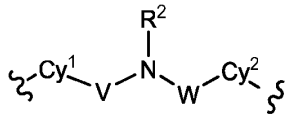
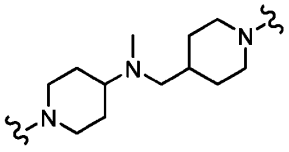
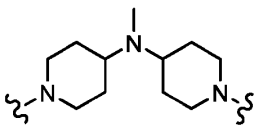
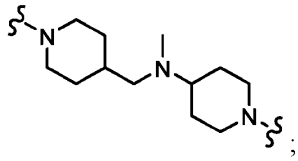
V and **W** are each independently absent or $-CH_2-$;

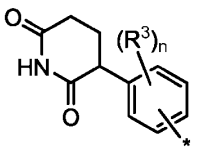
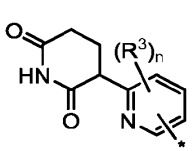
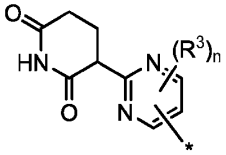
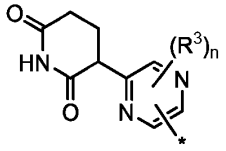
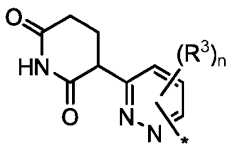
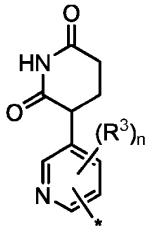
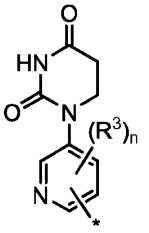
R^1 is a substituted or an unsubstituted C_1-C_6 alkyl;

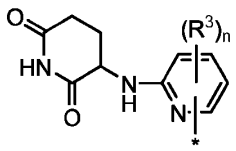
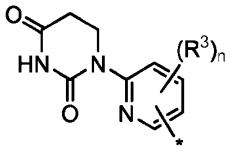
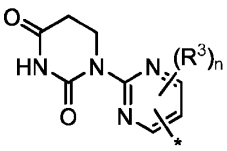
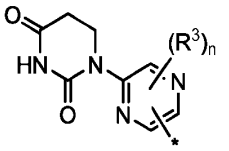
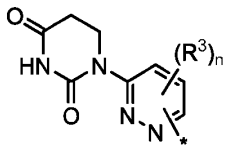
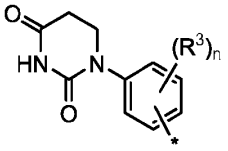
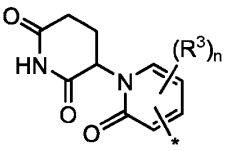
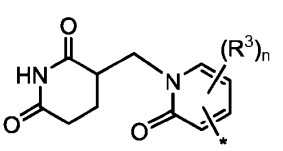
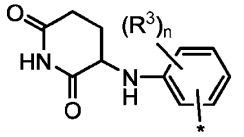
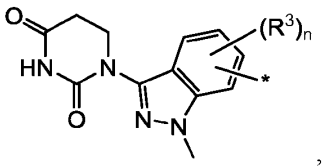
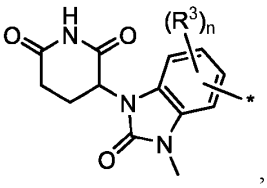
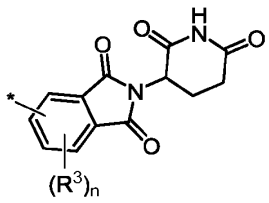
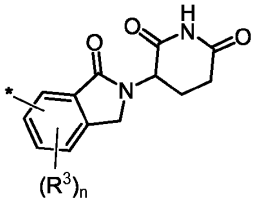
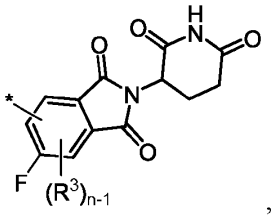
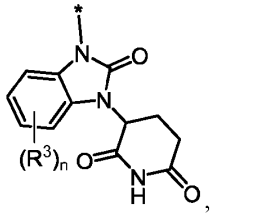
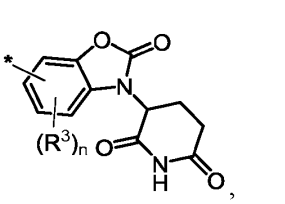
R^2 is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-C_xH_yD_z$; wherein:

x is an integer selected from 1, 2, 3 and 4;

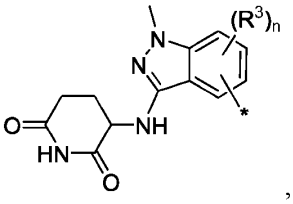
y is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7 and 8; and

z is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8 and 9; provided that the sum of **y** and **z** is 2**x** + 1 and with the proviso that  is not ,  or ;

L is , , , , , , ,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

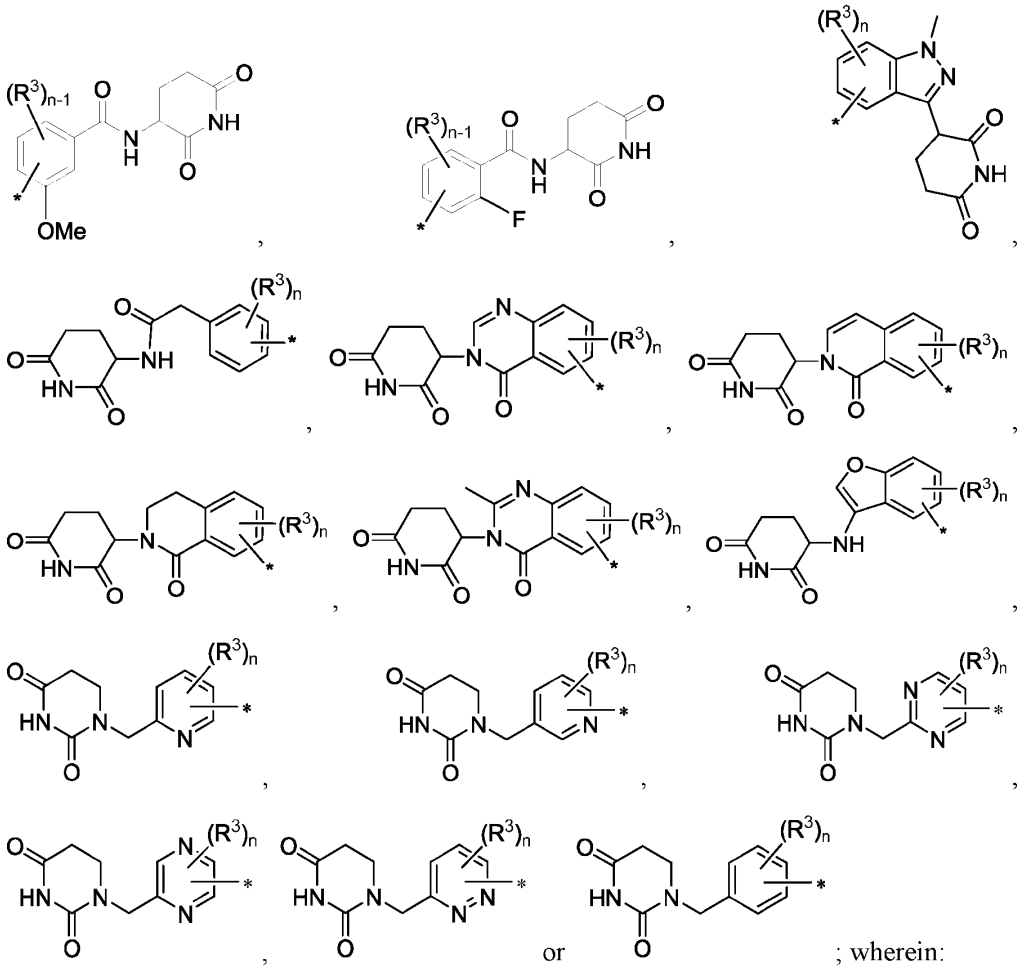
,

,

,

,

,



; wherein:

* indicates the point of attachment to **Cy^1**;

R^3 is halogen, C$_1$-C$_4$ alkyl, C$_1$-C$_4$ haloalkyl or C$_1$-C$_4$ alkoxy; and

n is 0, 1 or 2.

[0066] As defined above, the scope of heterocyclyl in Formula (I) or Formula (I') (including pharmaceutically acceptable salts thereof) refers to fully saturated heterocyclyls (but not partially saturated heterocyclyls) and includes spiro heterocyclyls, *e.g.*, a 7- or 8-membered spiro heterocyclyls.

[0067] In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **V** and **W** are both absent. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **V** is

absent and **W** is $-CH_2-$. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **V** is $-CH_2-$ and **W** is absent. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **V** and **W** are each $-CH_2-$. All other variables in Formula (I) or Formula (I'), are as described in any one of the above embodiments and in any one of the following embodiments.

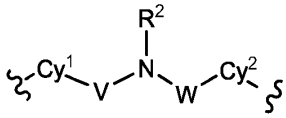
[0068] In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{Cy^1}$ and $\mathbf{Cy^2}$ are each independently an unsubstituted 4- to 11-membered heterocyclyl (*i.e.*, an unsubstituted 4-membered heterocyclyl, an unsubstituted 5-membered heterocyclyl, an unsubstituted 6-membered heterocyclyl, an unsubstituted 7-membered heterocyclyl, an unsubstituted 8-membered heterocyclyl, an unsubstituted 9-membered heterocyclyl, an unsubstituted 10-membered heterocyclyl or an unsubstituted 11-membered heterocyclyl) or a 4- to 11-membered heterocyclyl (*i.e.*, a 4-membered heterocyclyl, a 5-membered heterocyclyl, a 6-membered heterocyclyl, a 7-membered heterocyclyl, a 8-membered heterocyclyl, an unsubstituted 9-membered heterocyclyl, an unsubstituted 10-membered heterocyclyl or an unsubstituted 11-membered heterocyclyl) substituted with one or more groups selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy. As used herein, non-limiting examples of halogen include F, Cl and Br. Non-limiting examples of C_1-C_4 alkyl include methyl, ethyl, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-C(CH_3)_3$, $-CH_2CH(CH_3)_2$ and any other branched butyl. Non-limiting examples of C_1-C_4 haloalkyl and C_1-C_4 fluoroalkyl include $-CF_3$, $-CHF_2$, $-CFH_2$ and any C_2-C_4 alkyl substituted with 1, 2, 3, 4, or 5 fluoro atoms. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{Cy^1}$ and $\mathbf{Cy^2}$ are each independently an unsubstituted 4- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms and optionally 1 or 2 oxygen atoms or a 4- to 11-membered heterocyclyl and optionally 1 or 2 oxygen atoms containing 1 or 2 nitrogen atoms substituted with one or more groups selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{Cy^1}$ and $\mathbf{Cy^2}$ are each independently azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 2-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 2-azaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1-oxa-7-azaspiro[4.4]nonanyl, 5-oxa-2-

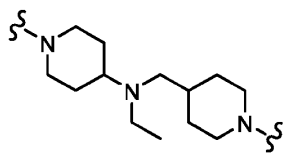
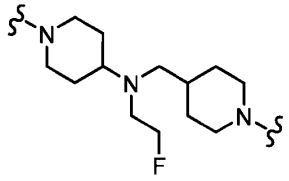
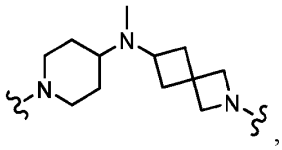
azaspiro[3.4]octanyl or 1-oxa-9-azaspiro[5.5]undecanyl, each optionally substituted with one or more groups selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy; for example F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** and **Cy^2** are each independently an unsubstituted 4- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms and 1 or 2 oxygen atoms or a 4- to 11-membered heterocyclyl and 1 or 2 oxygen atoms containing 1 or 2 nitrogen atoms substituted with one or more groups selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** and **Cy^2** are each independently an unsubstituted 4- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms or a 4- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms substituted with one or more groups selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** and **Cy^2** are each independently azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 2-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 2-azaspiro[3.4]octanyl or 2,6-diazaspiro[3.4]octanyl, each optionally substituted with one or more groups selected from F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** and **Cy^2** are each independently an unsubstituted 5- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms or a 5- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms substituted with one or more groups selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** and **Cy^2** are each independently pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 2-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 2-azaspiro[3.4]octanyl or 2,6-diazaspiro[3.4]octanyl, each optionally substituted with one or more groups selected from F, C_1-C_4 alkyl and C_1-C_4 fluoroalkyl. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** and **Cy^2** are each independently an unsubstituted 6- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms and optionally 1 or 2 oxygen atoms or a 6- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms and optionally 1 or 2 oxygen atoms substituted with one or more groups

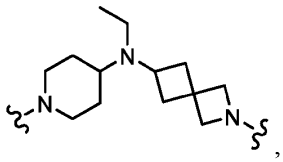
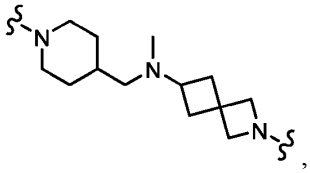
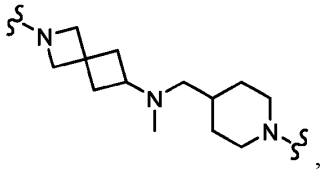
selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** and **Cy^2** are each independently an unsubstituted 6- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms and 1 or 2 oxygen atoms or a 6- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms and 1 or 2 oxygen atoms substituted with one or more groups selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** and **Cy^2** are each independently an unsubstituted 6- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms or a 6- to 8-membered heterocyclyl containing 1 or 2 nitrogen atoms substituted with one or more groups selected from halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** and **Cy^2** are each independently piperidinyl, piperazinyl, 2-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 2-azaspiro[3.4]octanyl or 2,6-diazaspiro[3.4]octanyl, each optionally substituted with one or more groups selected from F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** and **Cy^2** are each independently **Cy^1** is piperidinyl and **Cy^2** is 2-azaspiro[3.3]heptanyl, each optionally substituted with one or more groups selected from F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** and **Cy^2** are each piperidinyl, each optionally substituted with one or more groups selected from F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl and C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **Cy^1** is 2-azaspiro[3.3]heptanyl and **Cy^2** is piperidinyl, each optionally substituted with one or more groups selected from F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl and C_1-C_4 alkoxy. All other variables in Formula (I) or Formula (I'), are as described in any one of the above embodiments and in any one of the following embodiments.

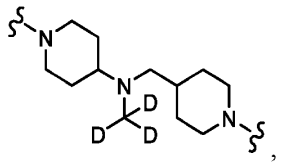
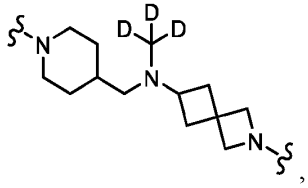
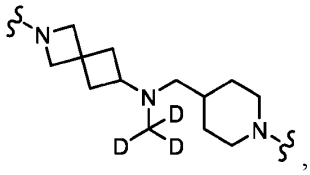
[0069] In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **R^2** is C_1-C_4 alkyl or $-C_xH_yD_z$. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **R^2** is $-C_xH_yD_z$. In one embodiment, in a compound of Formula (I) or Formula (I'), or a

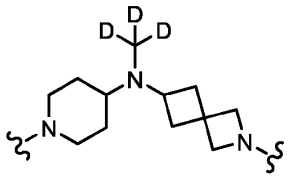
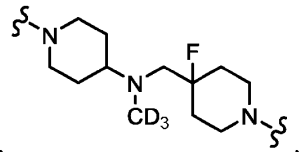
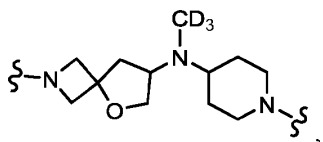
pharmaceutically acceptable salt thereof, $\mathbf{R^2}$ is $-CD_3$, $-CHD_2$, $-CDH_2$, $-C_2D_5$, $-C_2HD_4$, $-C_2H_2D_3$, $-C_2H_3D_2$ or $-C_2DH_4$. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^2}$ is C_1-C_2 alkyl, C_1-C_2 fluoroalkyl, $-CD_3$, $-CHD_2$, $-CDH_2$, $-C_2D_5$, $-C_2HD_4$, $-C_2H_2D_3$, $-C_2H_3D_2$ or $-C_2DH_4$. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^2}$ is $-CH_3$, $-C_2H_5$, $-C_2H_4F$ or $-CD_3$. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^2}$ is $-CD_3$. All other variables in Formula (I) or Formula (I'), are as described in any one of the above embodiments and in any one of the following embodiments.

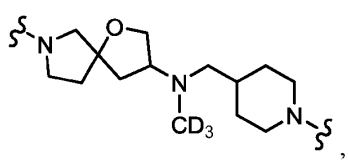
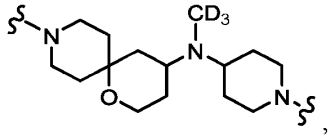
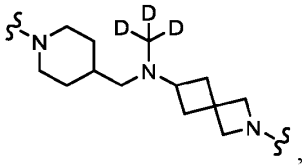
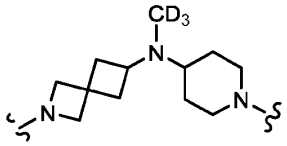
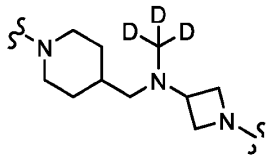
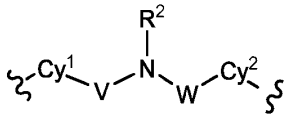
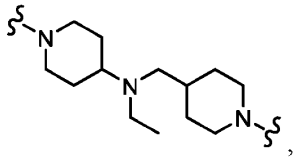
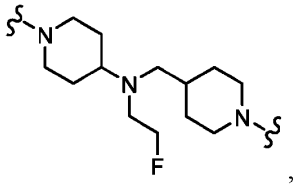
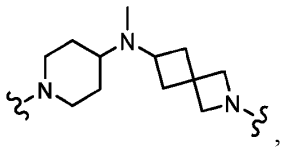
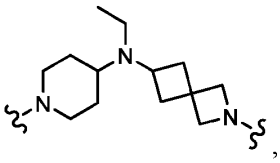
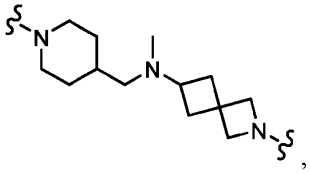
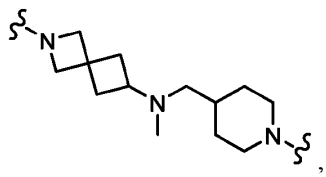
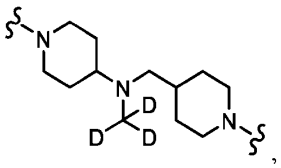
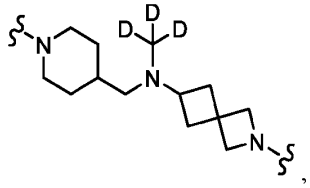
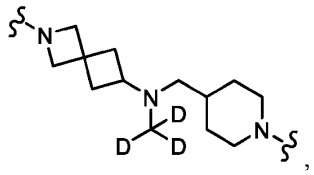
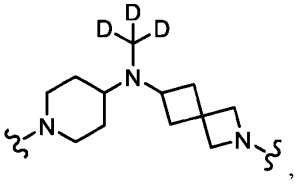
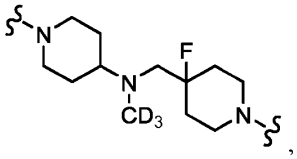
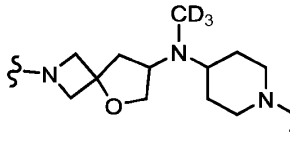
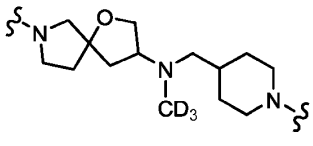
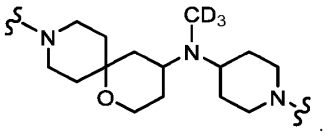
[0070] In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is

, , ,

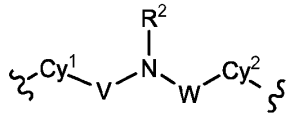
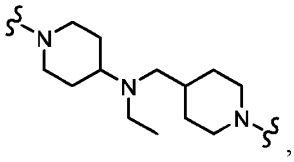
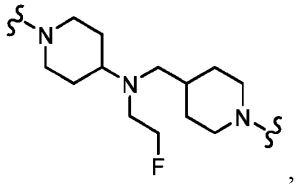
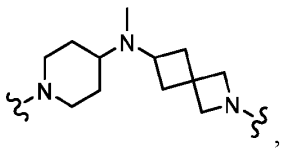
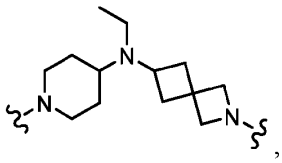
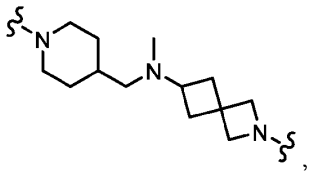
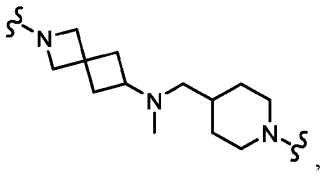
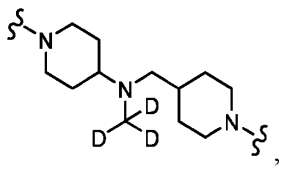
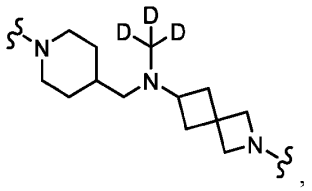
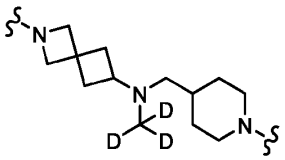
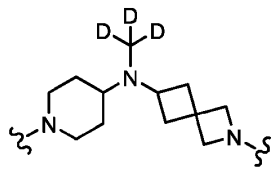
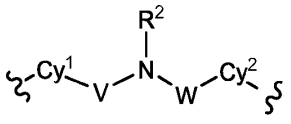
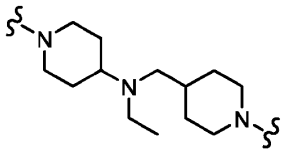
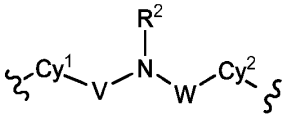
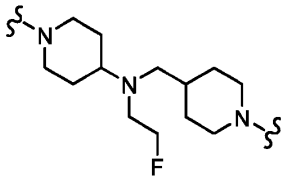
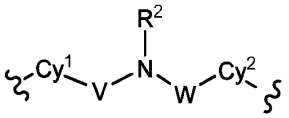
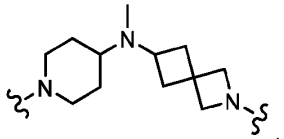
, , ,

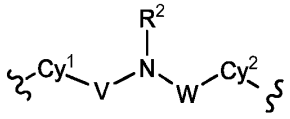
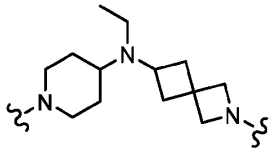
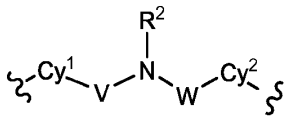
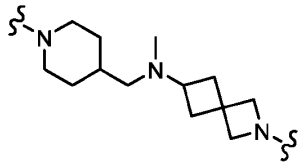
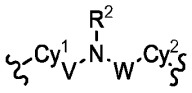
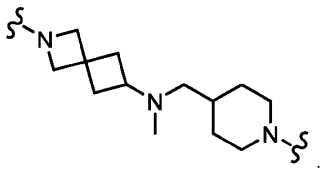
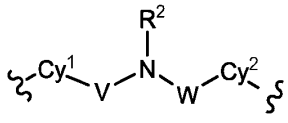
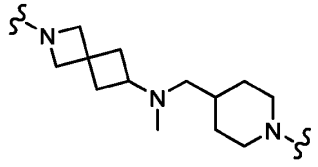
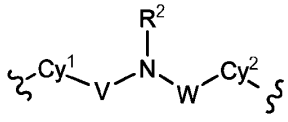
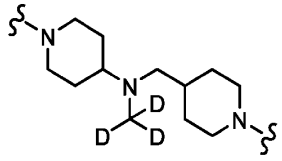
, , ,

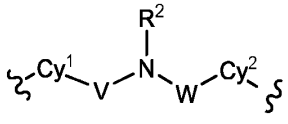
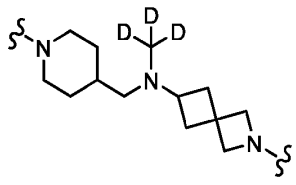
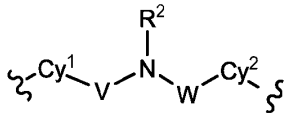
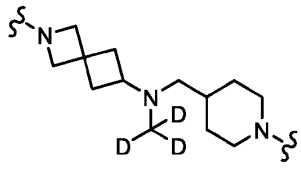
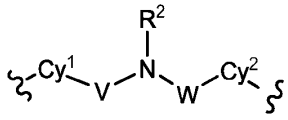
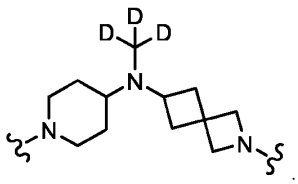
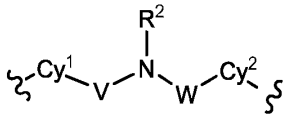
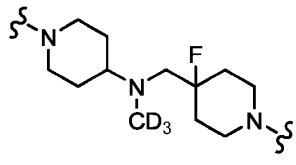
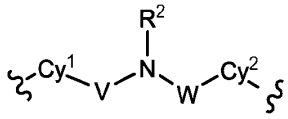
, , ,

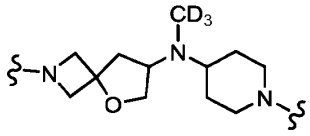
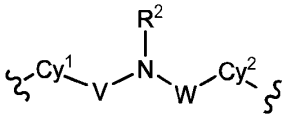
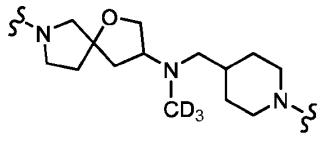
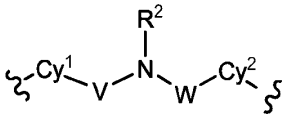
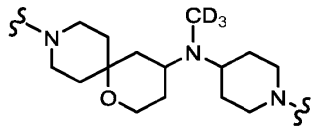
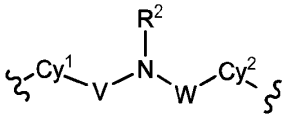
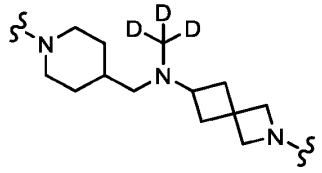
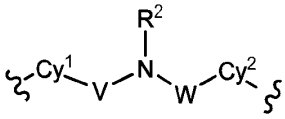
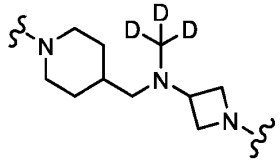
, , ,  or . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is , , , , , , , , , , , ,  or .

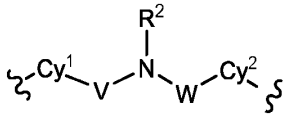
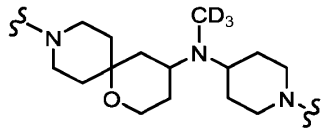
In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically

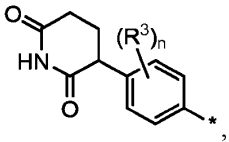
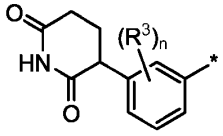
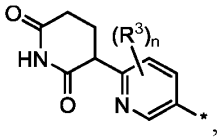
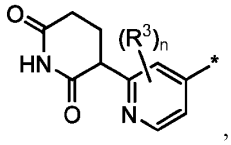
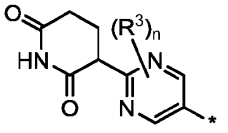
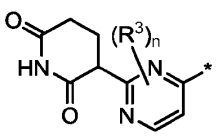
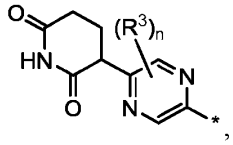
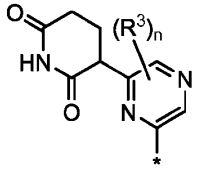
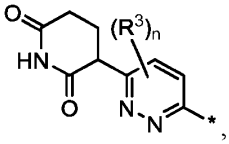
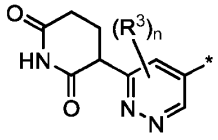
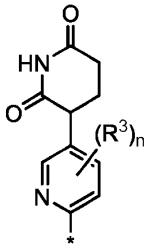
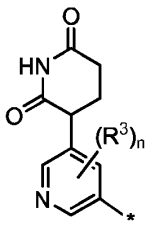
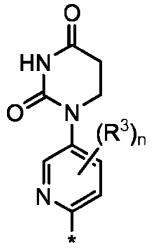
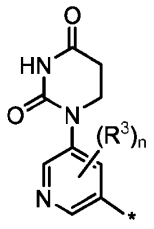
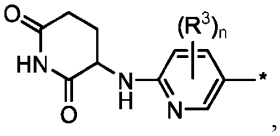
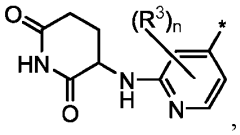
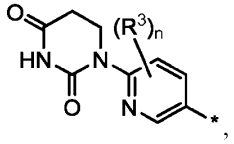
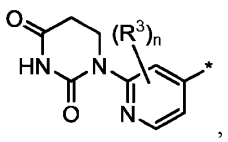
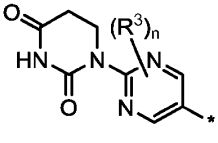
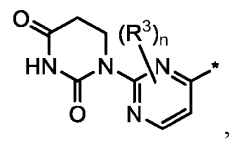
acceptable salt thereof,  is , , , , , , , ,  or . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,

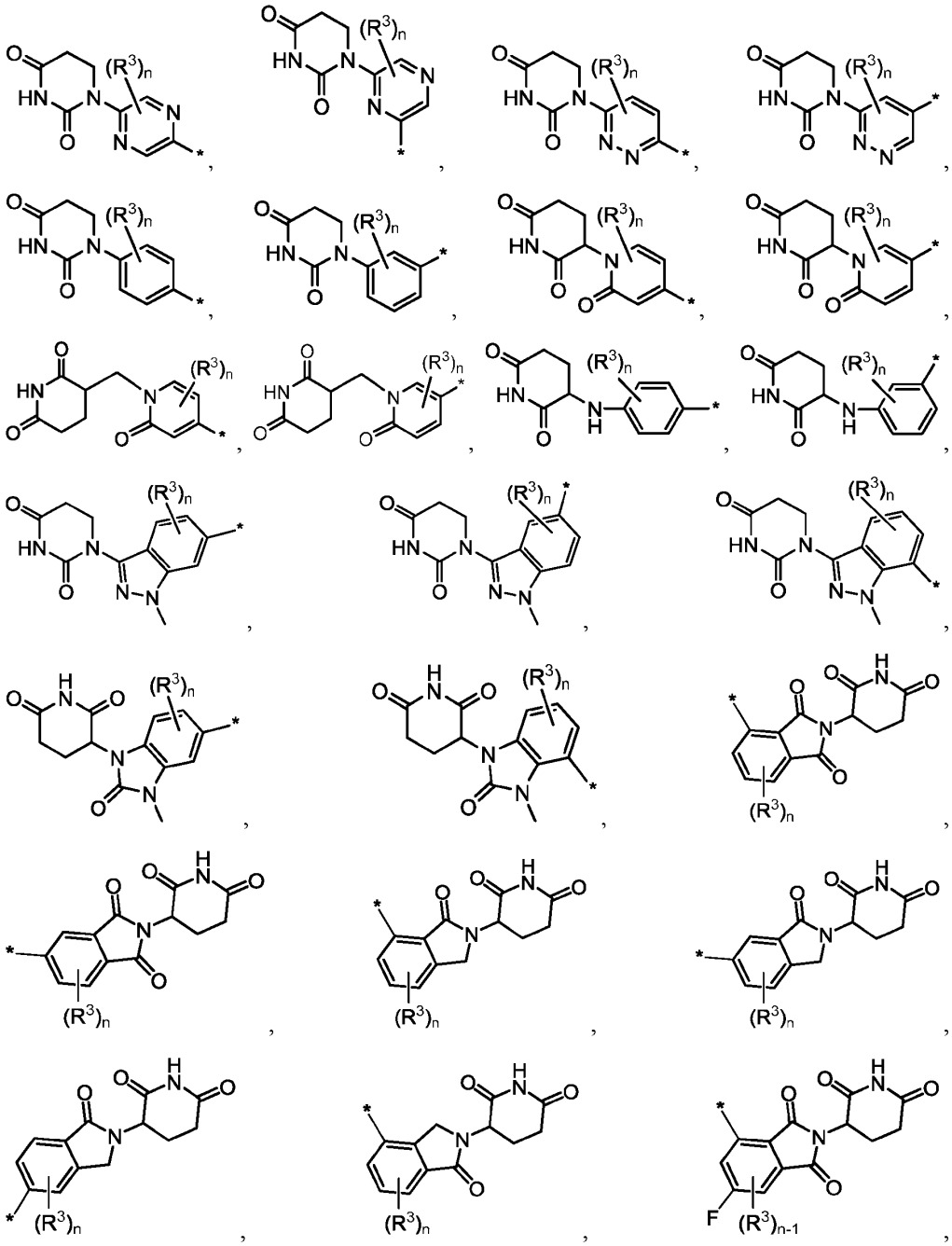
 is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is . In one embodiment, in a compound of Formula (I) or Formula (I'),

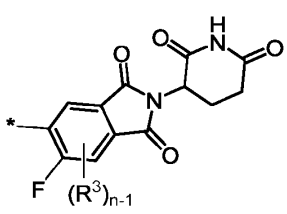
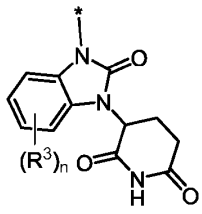
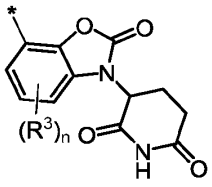
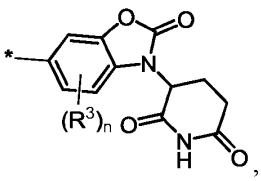
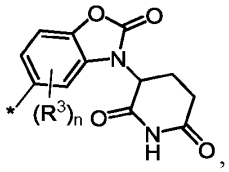
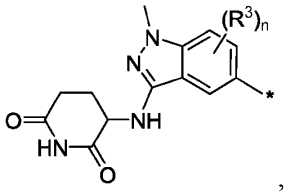
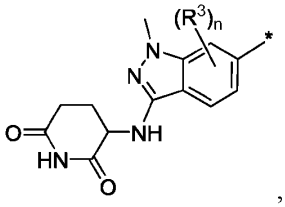
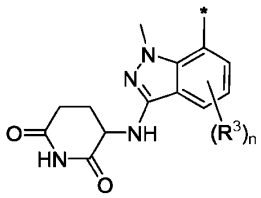
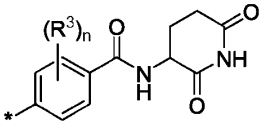
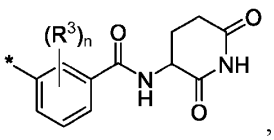
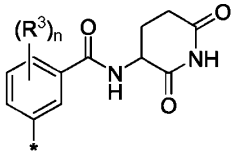
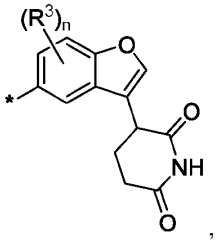
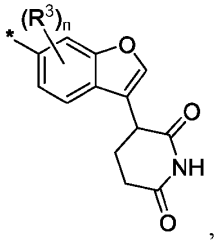
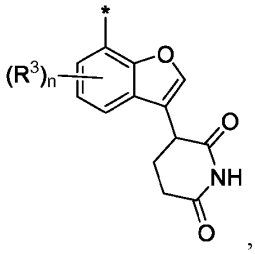
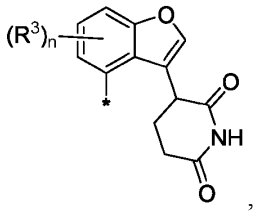
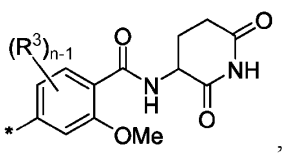
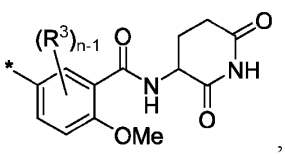
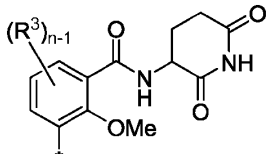
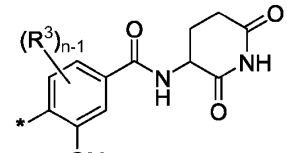
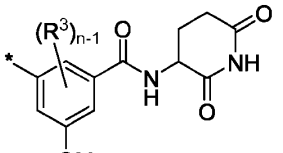
or a pharmaceutically acceptable salt thereof,  is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is


. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is 
. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is 
. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is 
. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof,  is 
. In one embodiment, in a compound of Formula (I) or Formula (I'),

or a pharmaceutically acceptable salt thereof,  is . All other variables in Formula (I) or Formula (I'), are as described in any one of the above embodiments and in any one of the following embodiments.

[0071] In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is , , , , , , , , , , , , , , , , , , , .

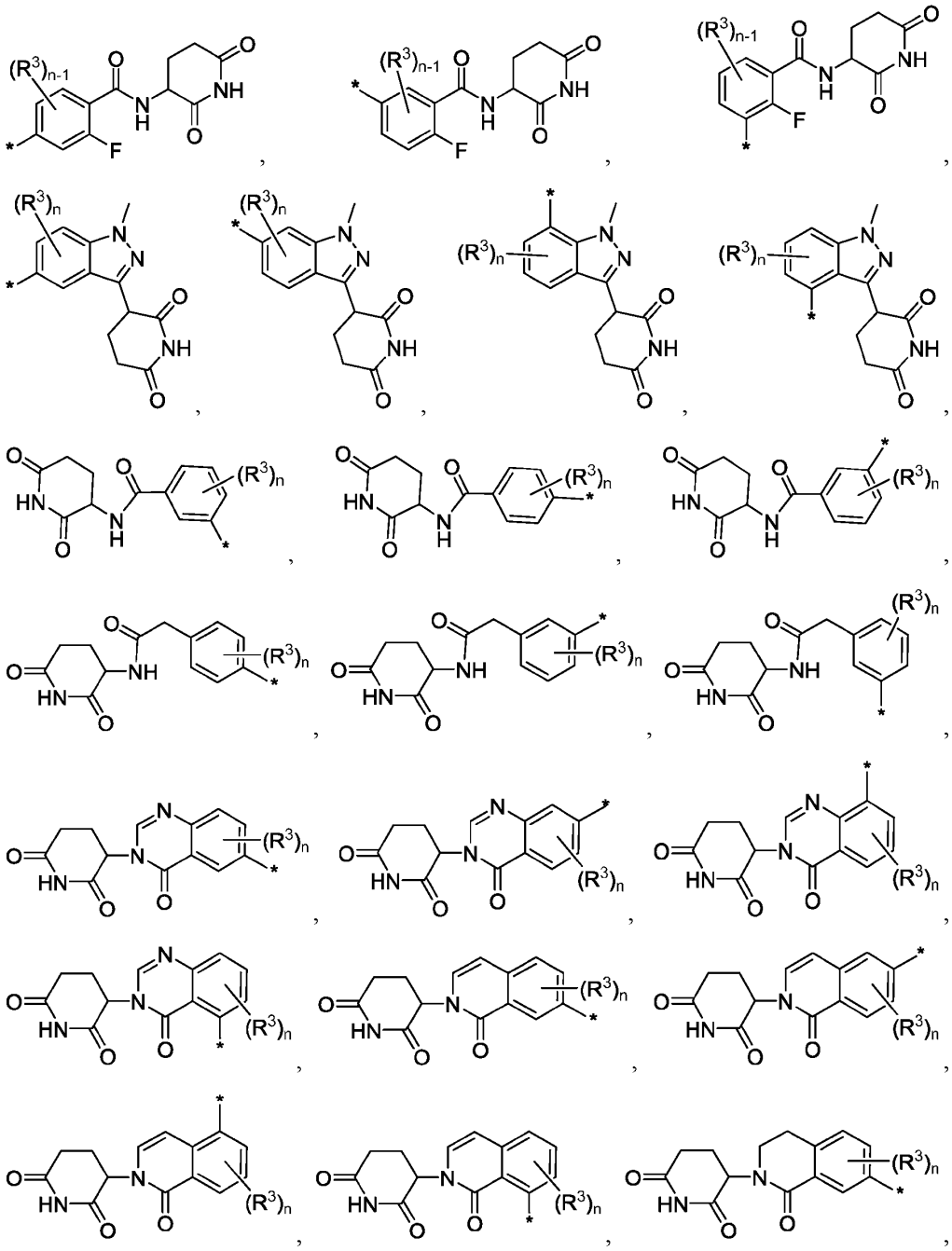


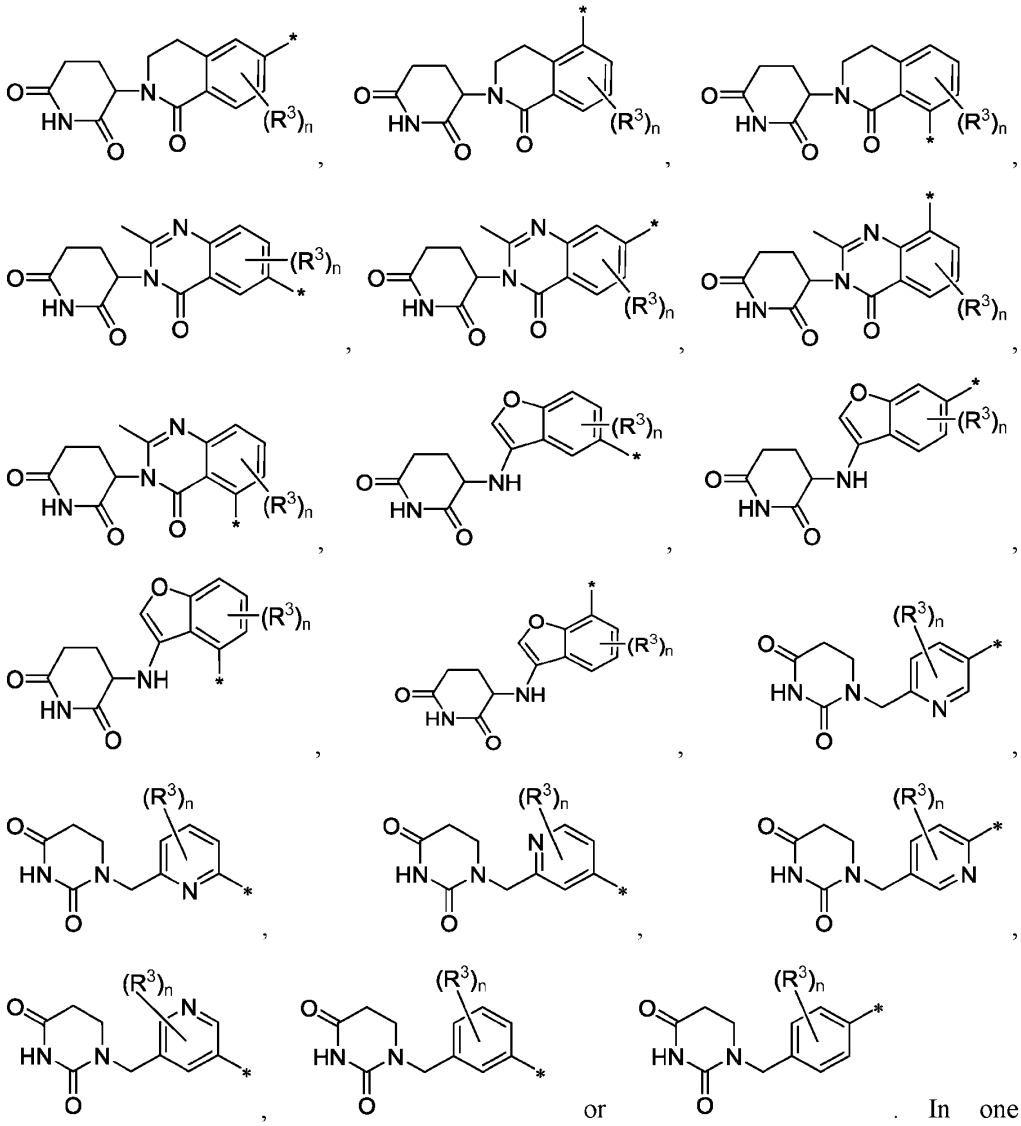

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

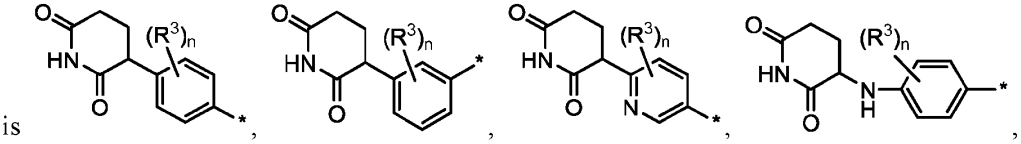
,

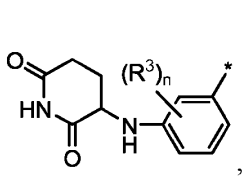
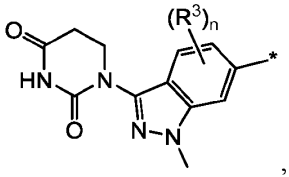
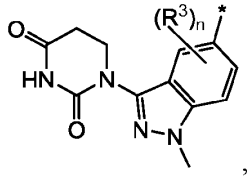
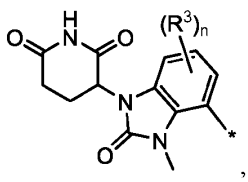
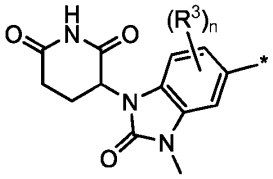
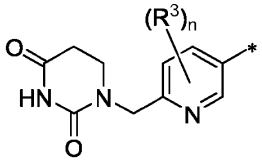
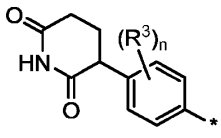
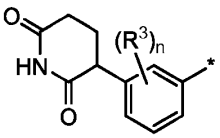
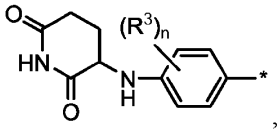
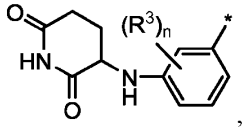
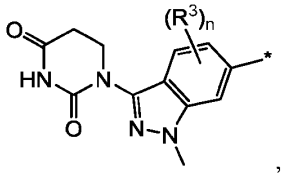
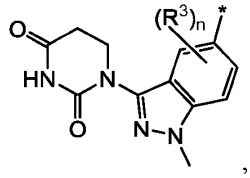
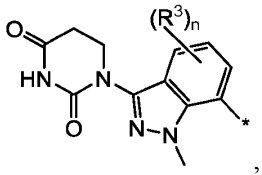
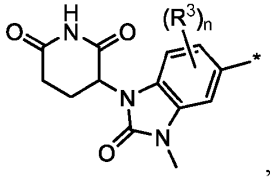
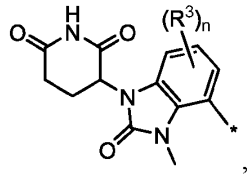
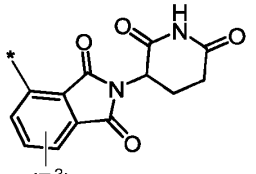
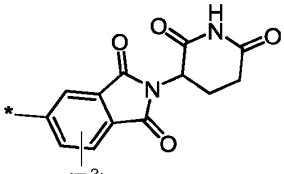
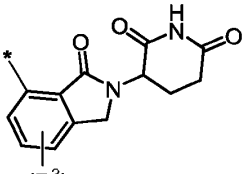
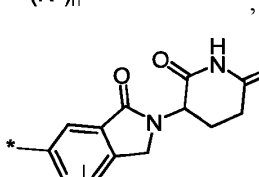
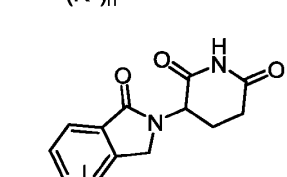
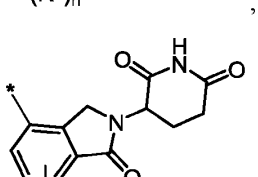
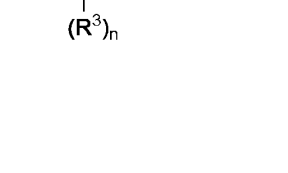
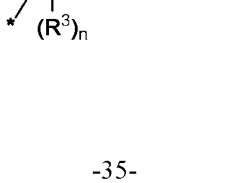
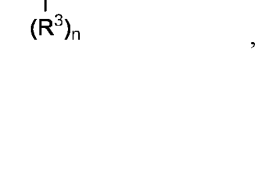
,

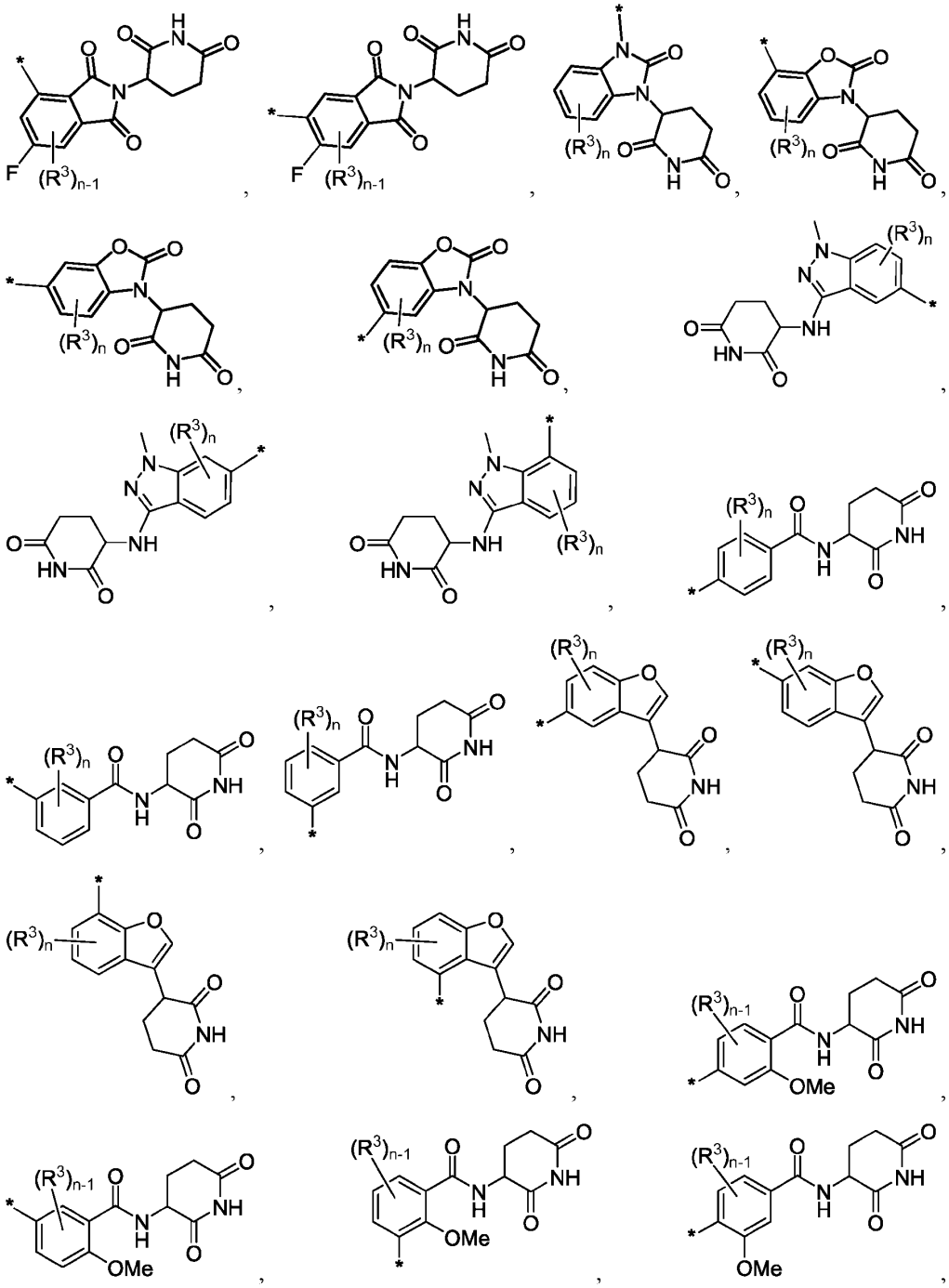


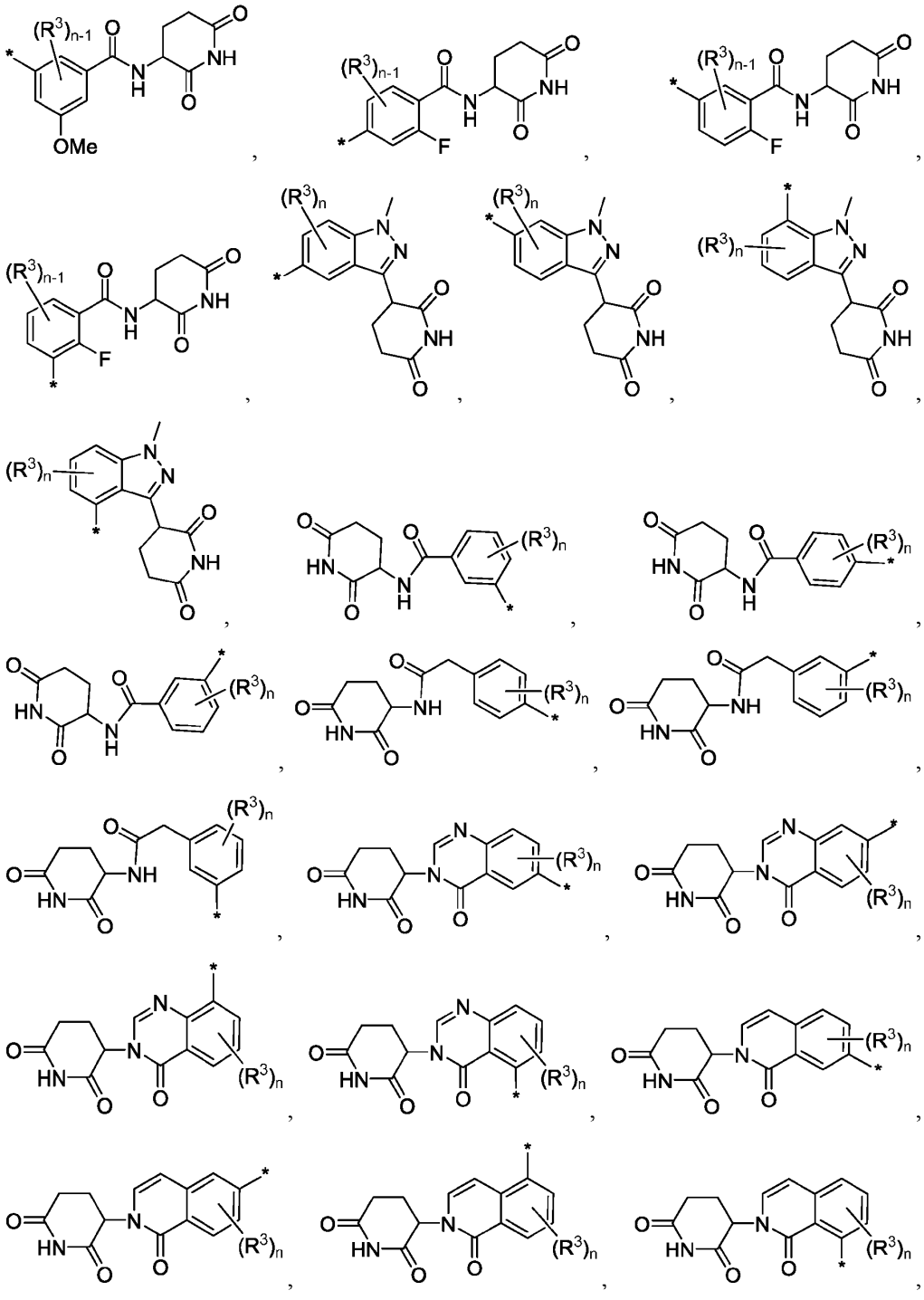


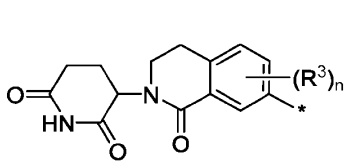
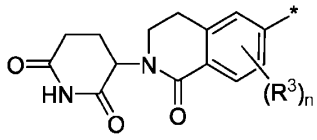
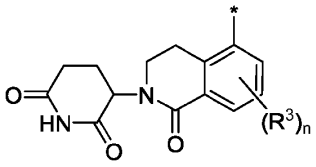
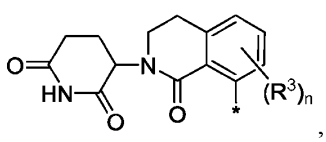
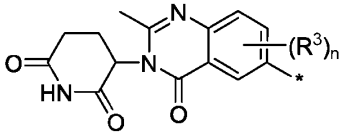
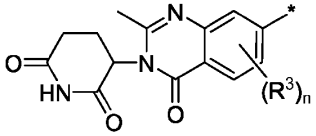
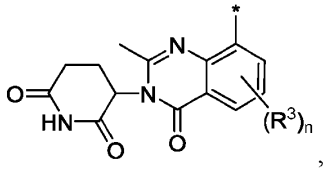
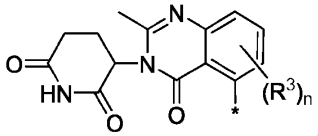
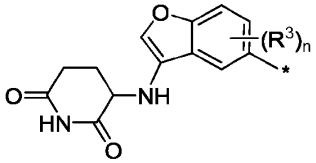
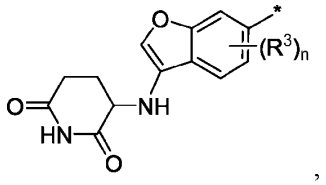
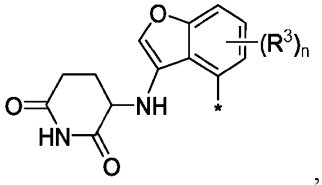
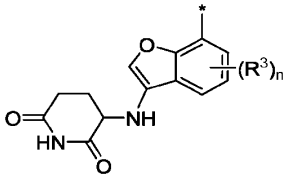
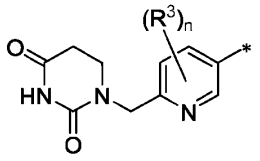
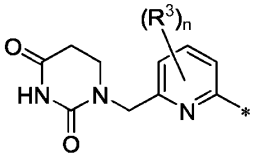
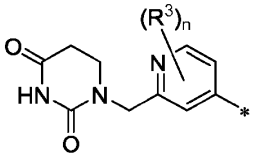
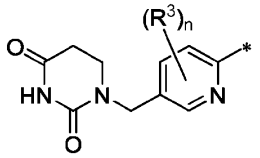
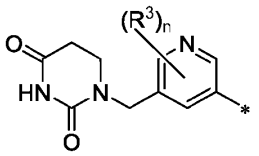
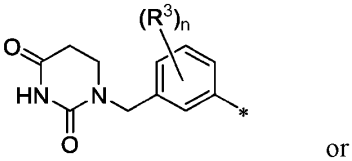
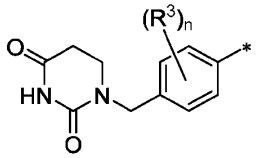
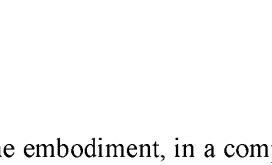
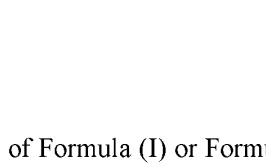
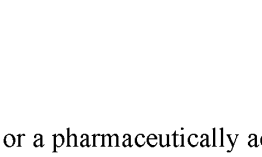
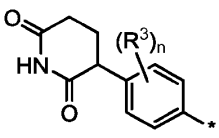
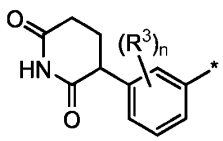
embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is

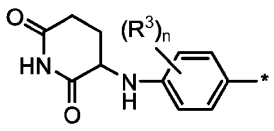
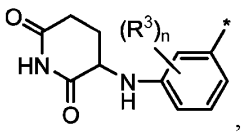
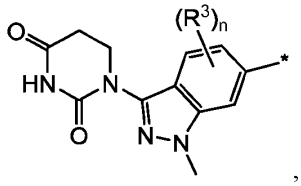
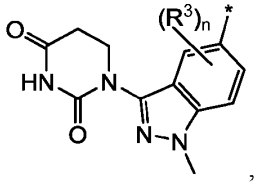
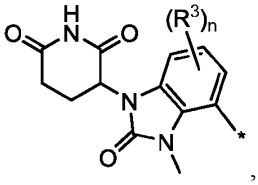
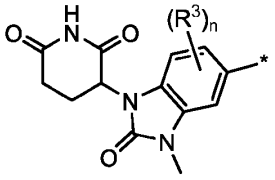
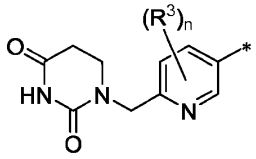
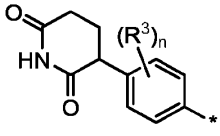
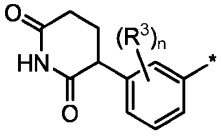
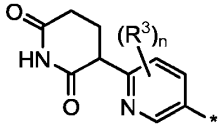
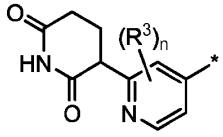
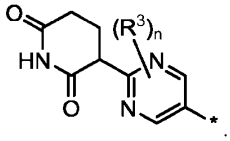


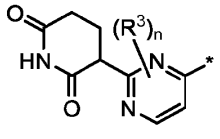
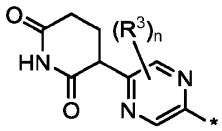
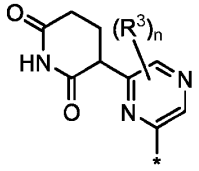
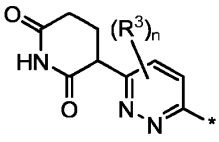
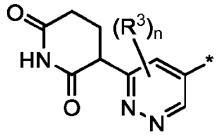
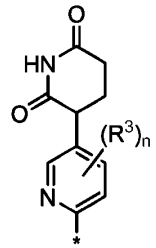
, , , ,  or . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is , , , , , , , , , , , , , , , , , .

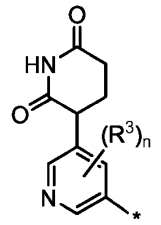


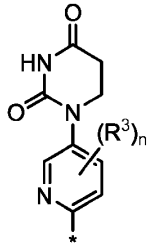
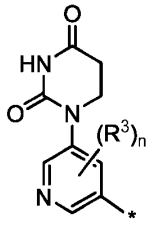
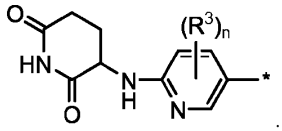
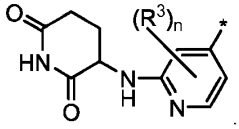
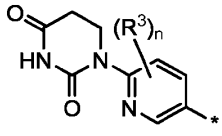


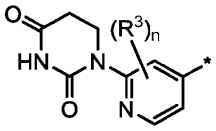
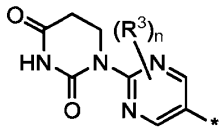
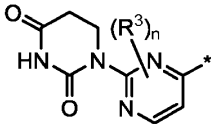
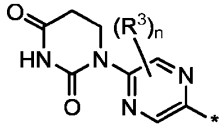
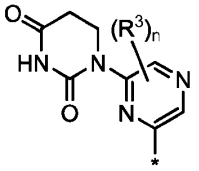
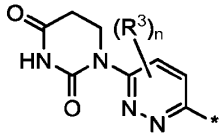
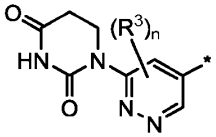
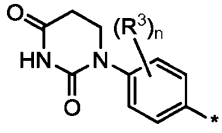

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

or

. In one embodiment, in a compound of Formula (I) or Formula (I'),
or a pharmaceutically acceptable salt thereof, **L** is

,

,

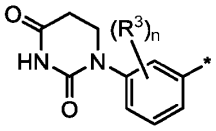
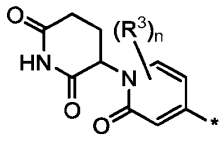
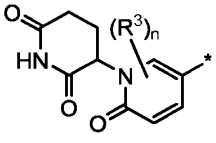
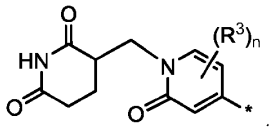
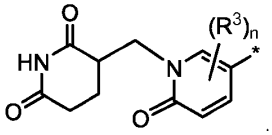
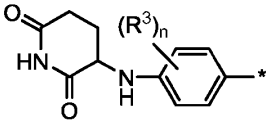
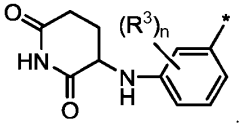
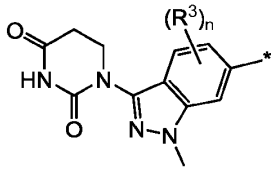

,

,

,

,

,

or

. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is

. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is

. In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is

. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is

. In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is

. In one embodiment, in a

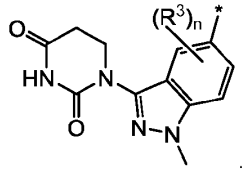
compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a

compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is .

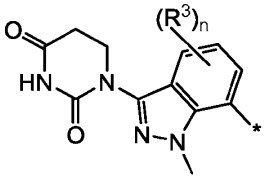
In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a

pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a

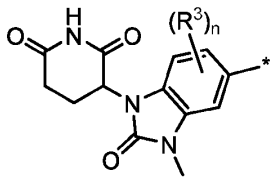
pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I)



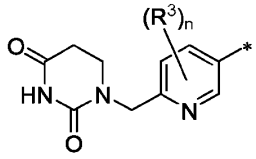
or Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically



acceptable salt thereof, **L** is . In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **L** is



. In one embodiment, in a compound of Formula (I) or Formula (I'),



or a pharmaceutically acceptable salt thereof, **L** is . All other variables in Formula (I) or Formula (I'), are as described in any one of the above embodiments and in any one of the following embodiments.

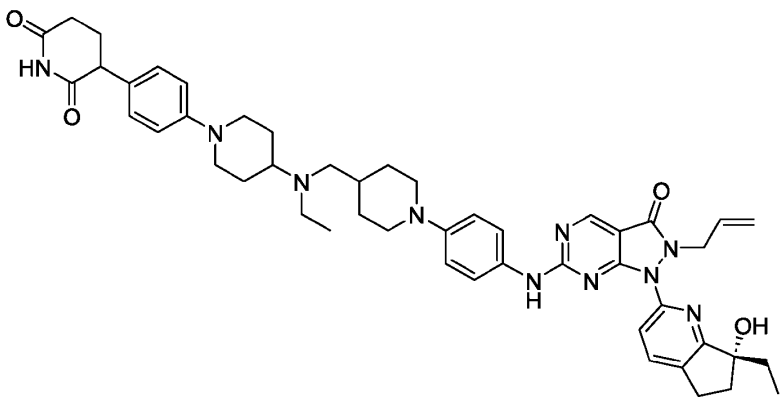
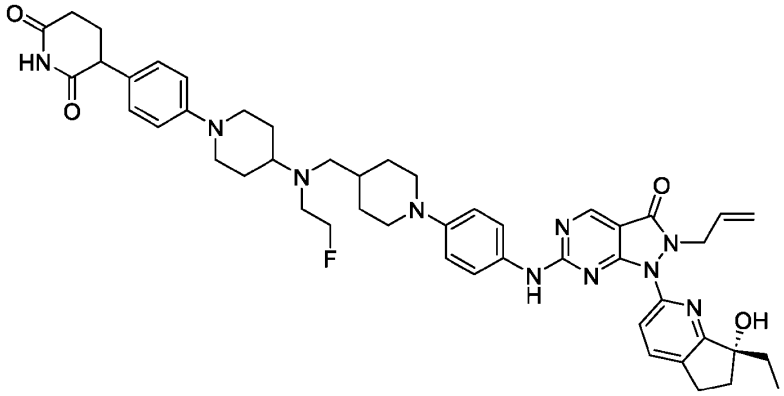
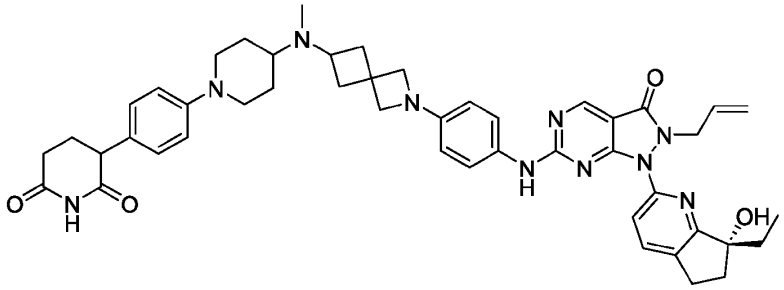
[0072] In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^3}$ is halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl or C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^3}$ is F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl or C_1-C_4 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^3}$ is F, C_1-C_2 alkyl, C_1-C_2 fluoroalkyl or C_1-C_2 alkoxy. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^3}$ is F. All other variables in Formula (I) or Formula (I'), are as described in any one of the above embodiments and in any one of the following embodiments.

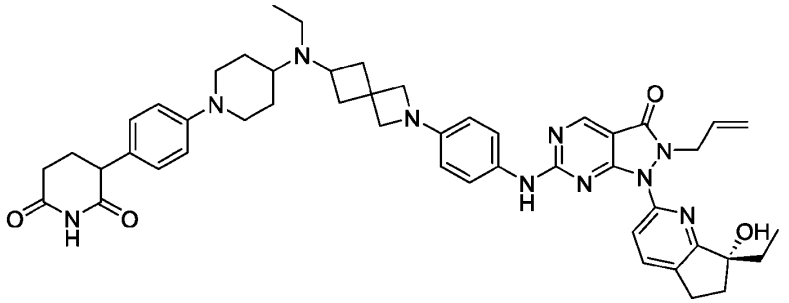
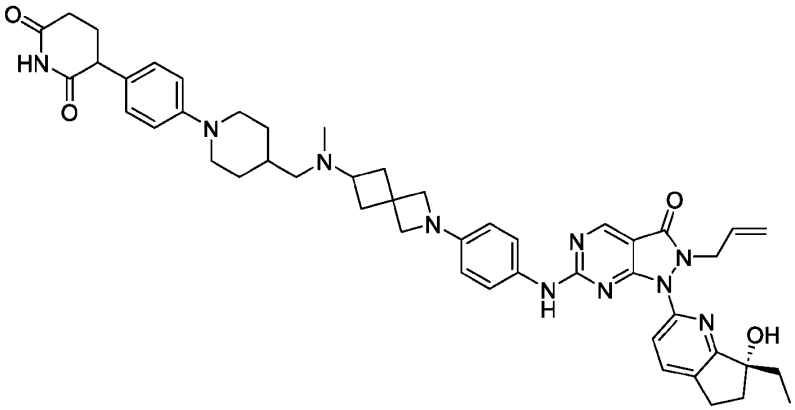
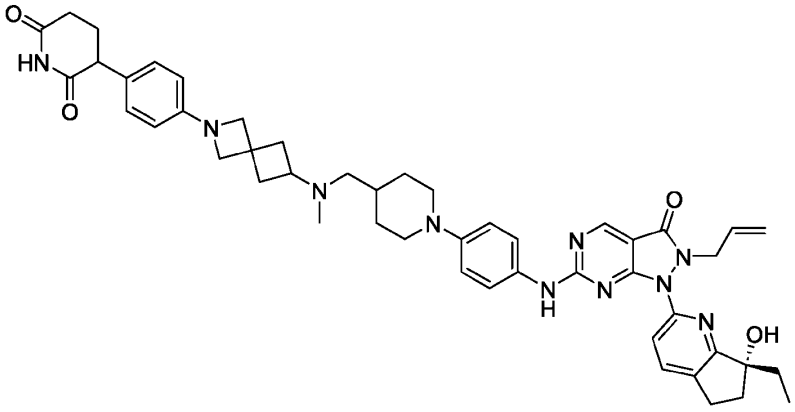
[0073] In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **n** is 0 or 1. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **n** is 0. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, **n** is 1. All other variables in Formula (I) or Formula (I'), are as described in any one of the above embodiments and in any one of the following embodiments.

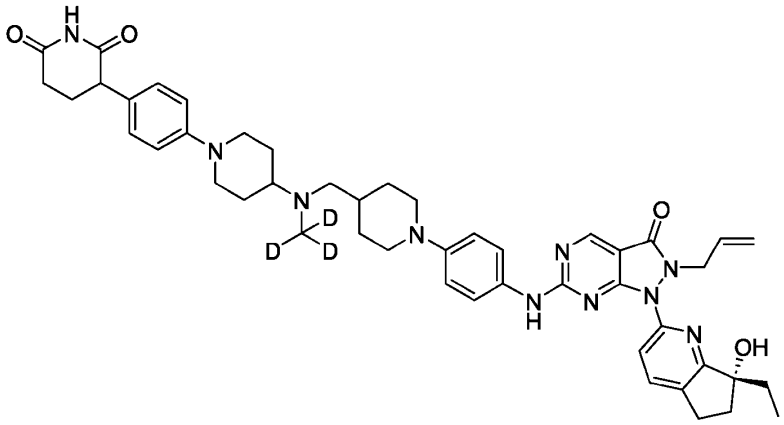
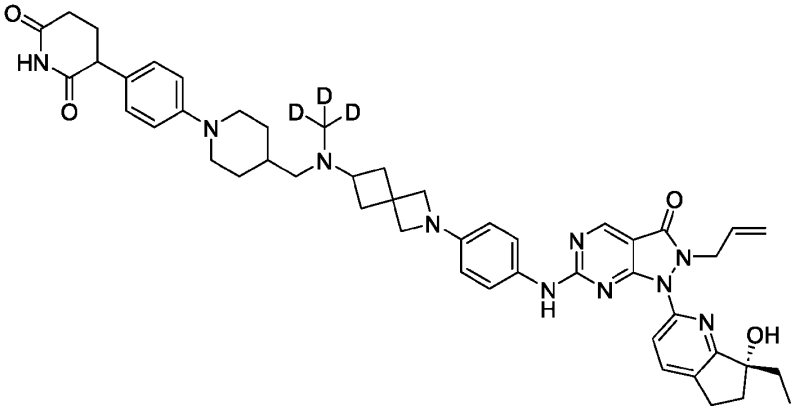
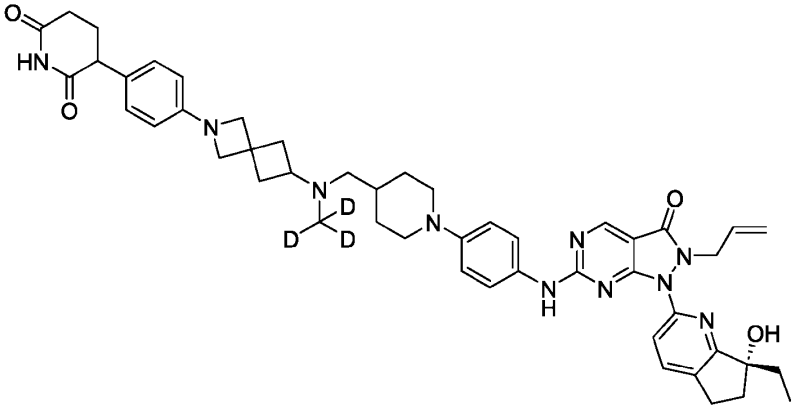
[0074] In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is C_1-C_4 alkyl or C_1-C_4 haloalkyl. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is C_1-C_4 alkyl or C_1-C_4 fluoroalkyl. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is C_1-C_2 alkyl or C_1-C_2 fluoroalkyl. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is methyl. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is ethyl. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is $-CF_3$. In one embodiment, in a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, $\mathbf{R^1}$ is $-CHF_2$. All other variables in Formula (I) or Formula (I'), are as described in any one of the above embodiments and in any one of the following embodiments.

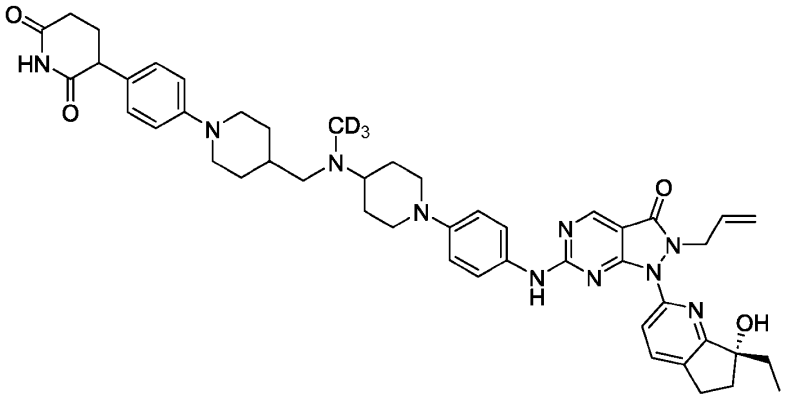
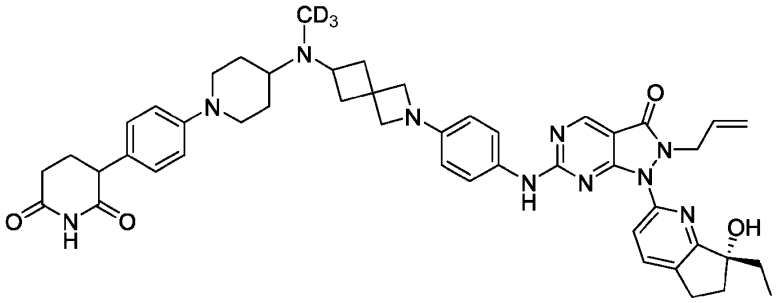
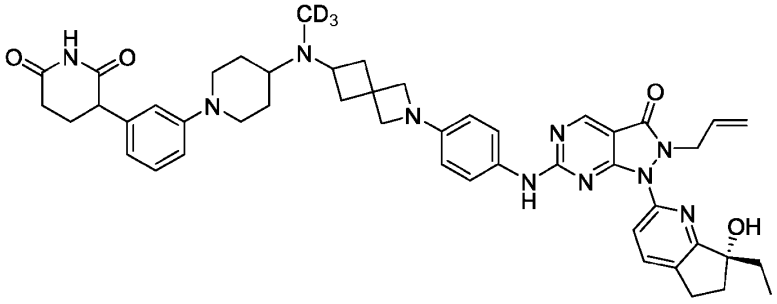
[0075] Various embodiments provide a compound (e.g., a compound of Formula (I) or Formula (I')), or a pharmaceutically acceptable salt thereof, wherein the compound has a structure selected from those of Compound Nos. 1 to 36 as listed in the following Table 1:

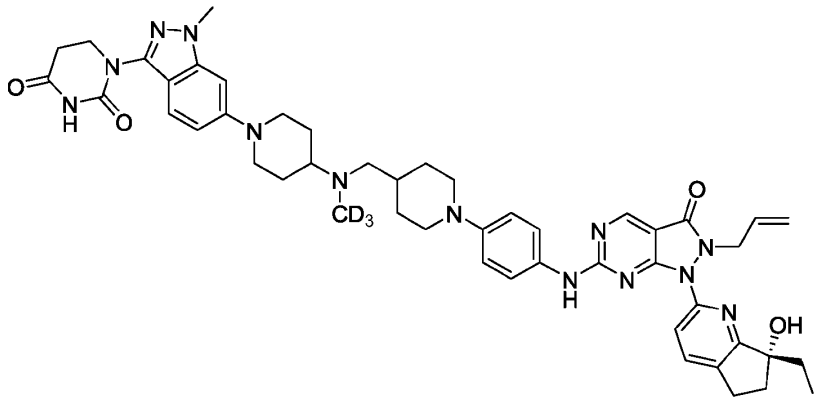
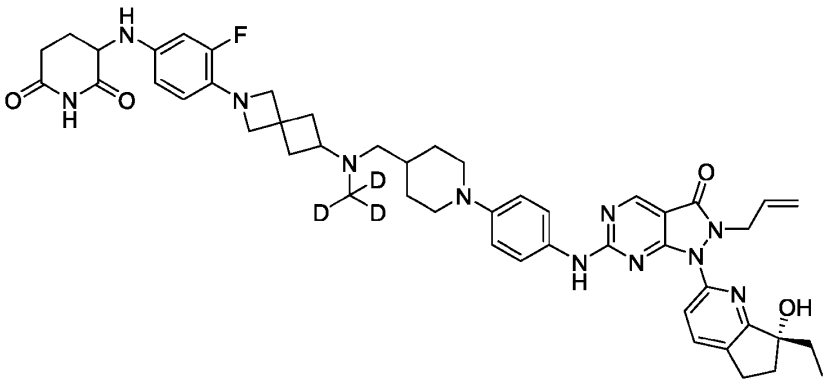
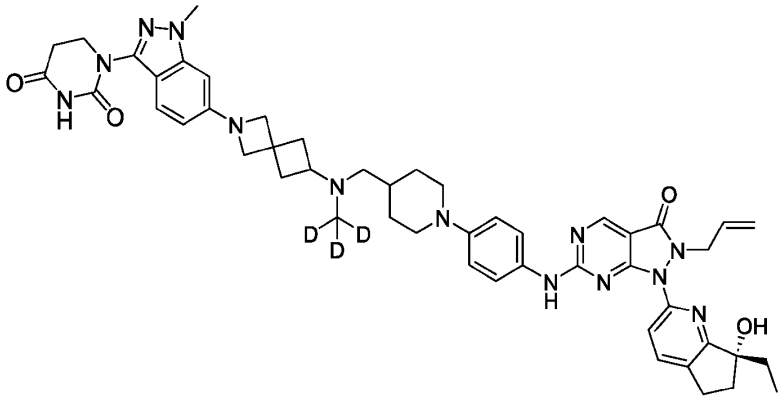
Table 1. Exemplary Compound Nos. 1 to 36.

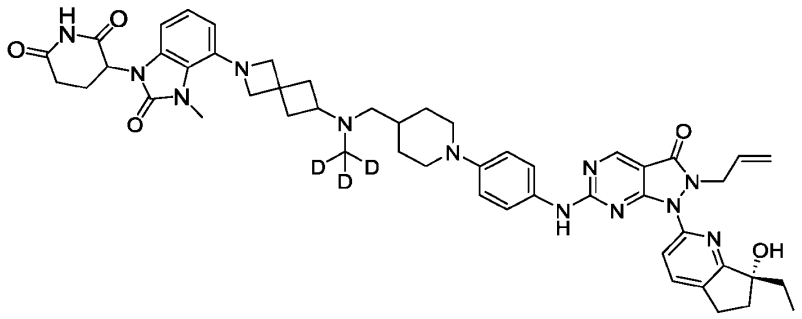
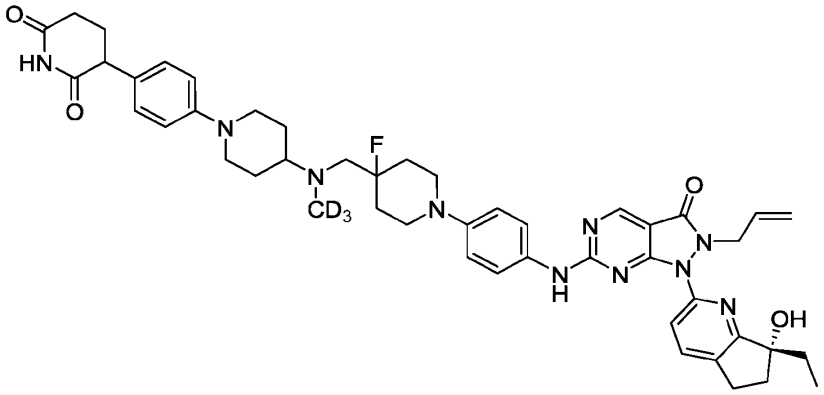
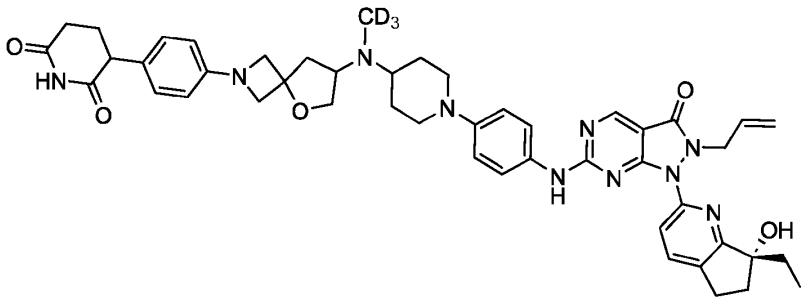
Compound No.	Structure
1	
2	
3	

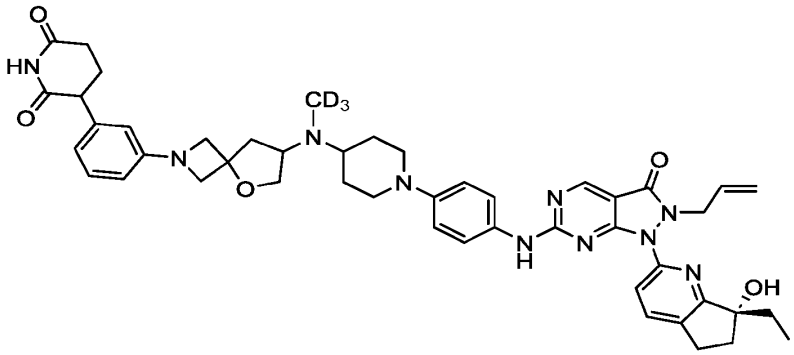
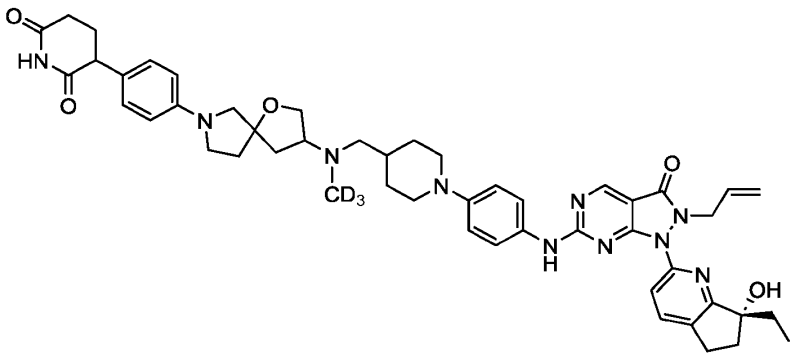
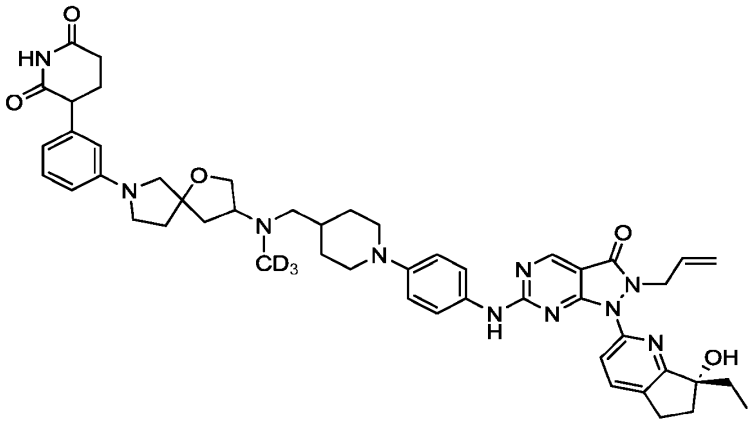
Compound No.	Structure
4	
5	
6	

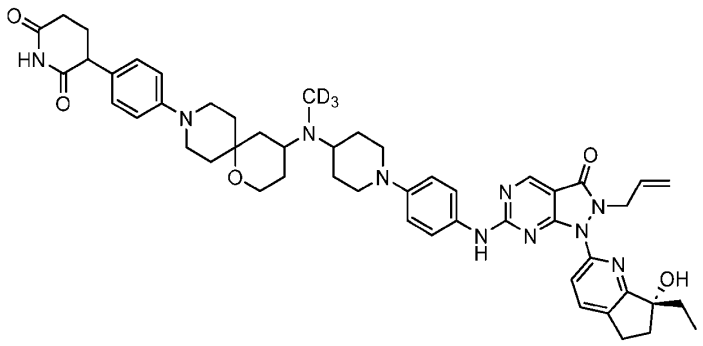
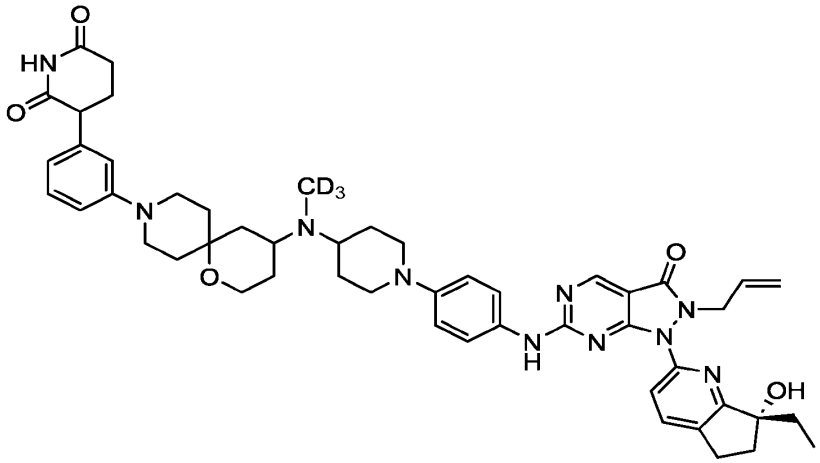
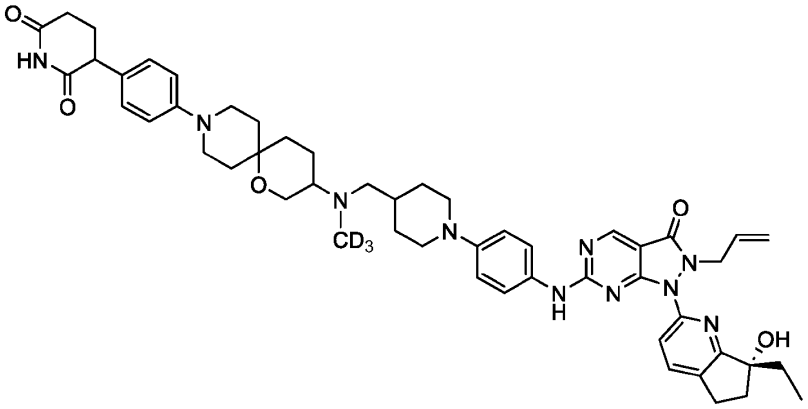
Compound No.	Structure
7	
8	
9	

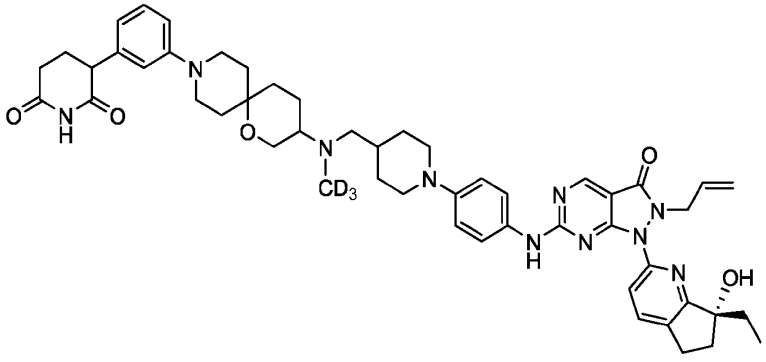
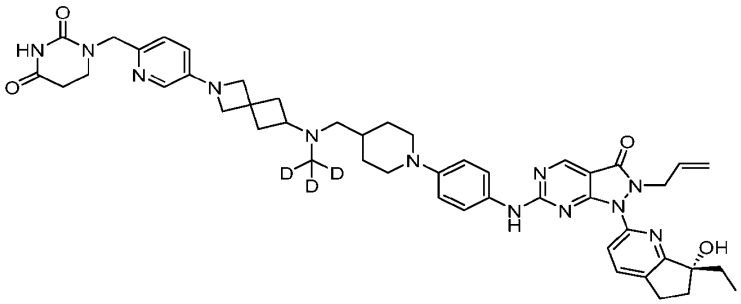
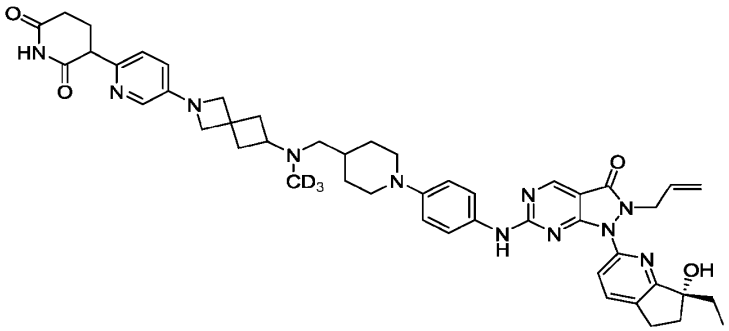
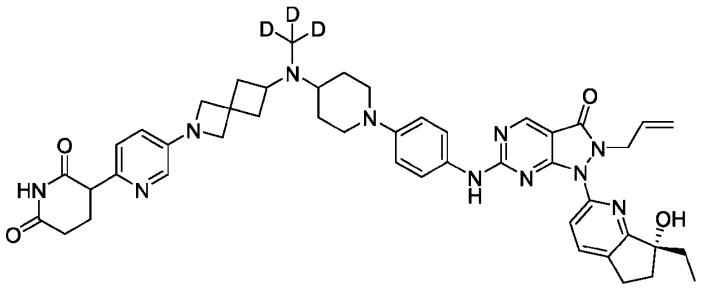
Compound No.	Structure
10	
11	
12	

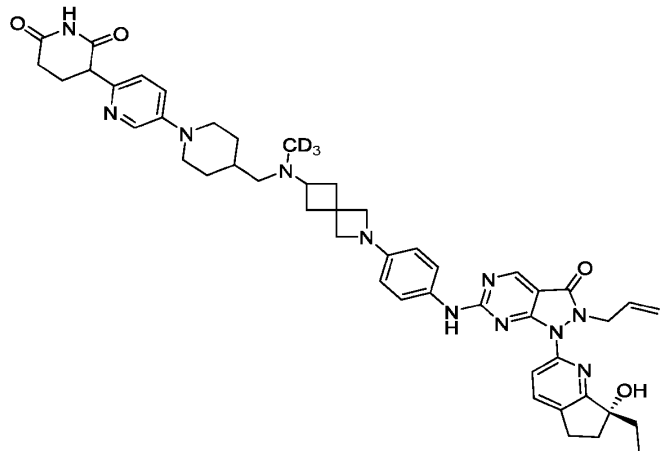
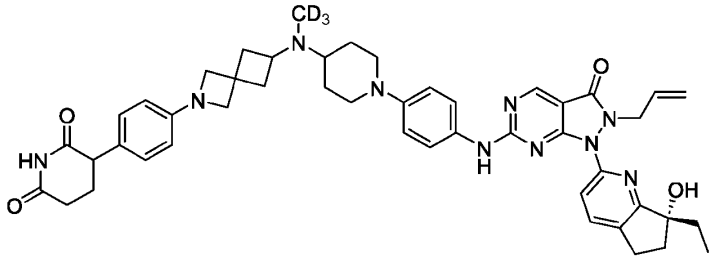
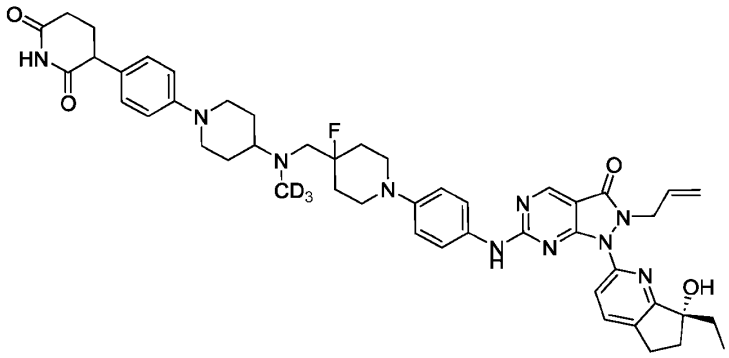
Compound No.	Structure
13	
14	
15	

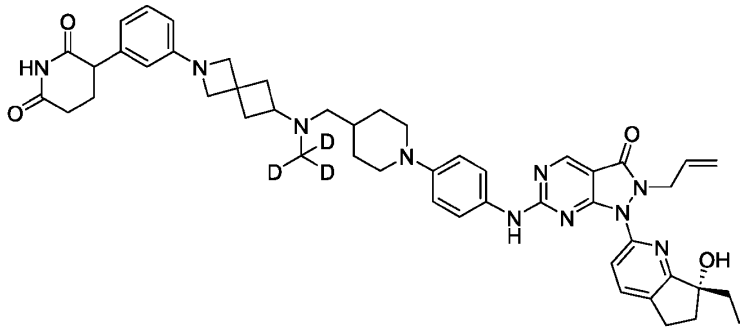
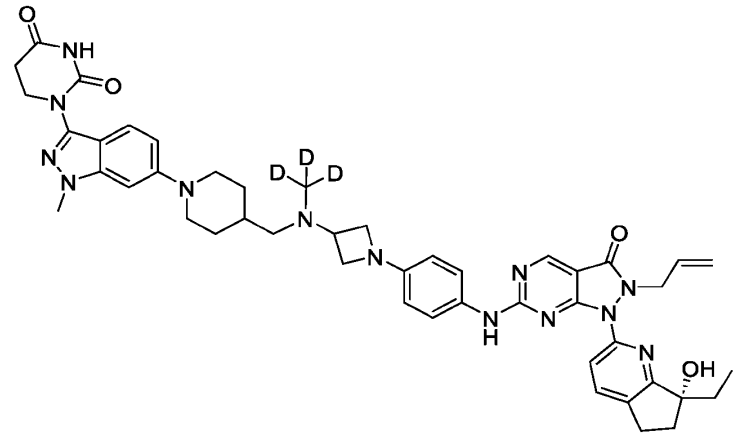
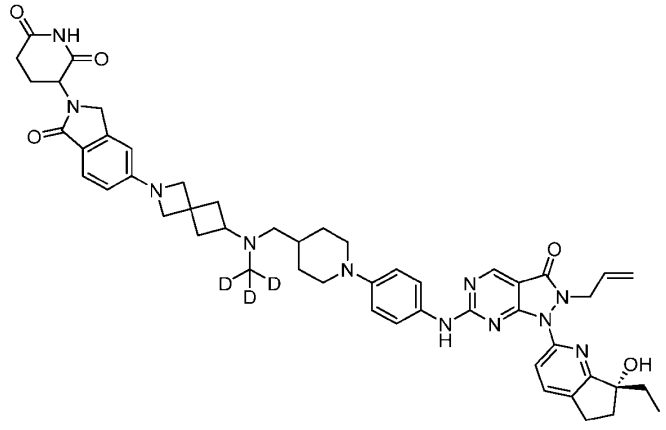
Compound No.	Structure
16	
17	
18	

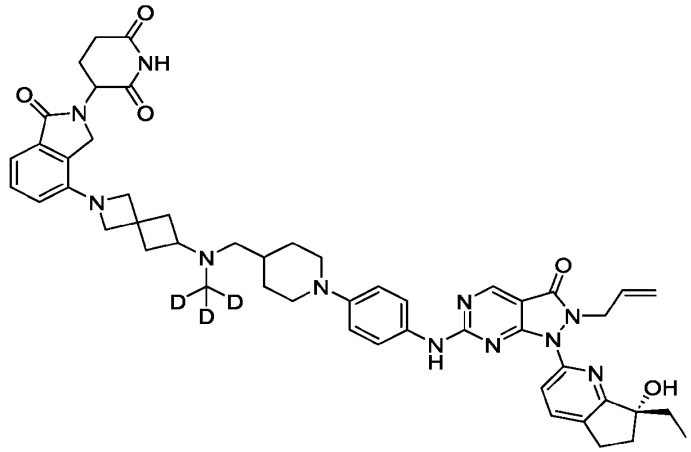
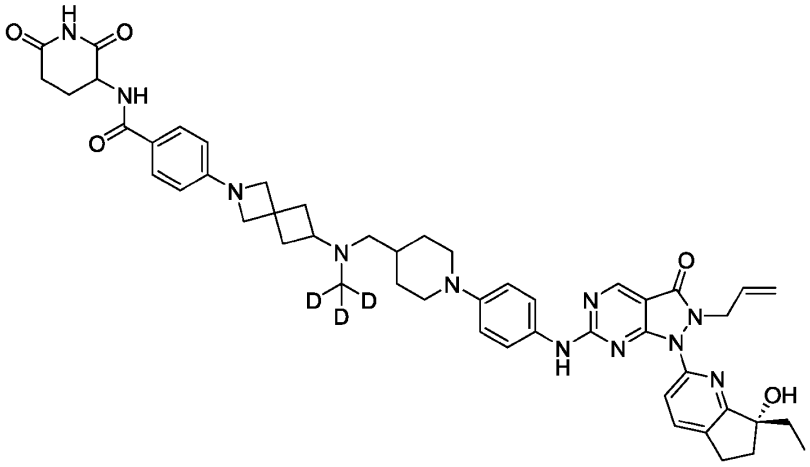
Compound No.	Structure
19	
20	
21	

Compound No.	Structure
22	
23	
24	

Compound No.	Structure
25	
26	
27	
28	

Compound No.	Structure
29	
30	
31	

Compound No.	Structure
32	
33	
34	

Compound No.	Structure
35	
36	

Synthesis

[0076] Compounds of Formula (I) or Formula (I'), or pharmaceutically acceptable salts thereof, can be made in various ways by those skilled using known techniques as guided by the detailed teachings provided herein, including the Examples provided below. For example, in an embodiment, compounds of the Formula (I) are prepared in accordance with the procedures illustrated in General Scheme A provided herein. Any preliminary reaction steps required to form starting compounds or other precursors, can be carried out by those skilled in the art, for example by appropriate adjustment of the reagents and conditions

described in the Examples. In General Scheme A, the variables including Cy^1, Cy^2, V, W, R^1, R^2 and L can be as described elsewhere herein, taking into consideration the synthetic conversions involved as understood by those of skill in the art.

Pharmaceutical Compositions

[0077] Some embodiments described herein relate to a pharmaceutical composition, that can include an effective amount of one or more compounds described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0078] The term "pharmaceutical composition" refers to a mixture of one or more compounds and/or salts disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and salicylic acid. Pharmaceutical compositions will generally be tailored to the specific intended route of administration.

[0079] The term "physiologically acceptable" defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound nor cause appreciable damage or injury to an animal to which delivery of the composition is intended.

[0080] As used herein, a "carrier" refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[0081] As used herein, a "diluent" refers to an ingredient in a pharmaceutical composition that lacks appreciable pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A

common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the pH and isotonicity of human blood.

[0082] As used herein, an "excipient" refers to an essentially inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. For example, stabilizers such as anti-oxidants and metal-chelating agents are excipients. In an embodiment, the pharmaceutical composition comprises an anti-oxidant and/or a metal-chelating agent. A "diluent" is a type of excipient.

[0083] The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or carriers, diluents, excipients or combinations thereof. Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art.

[0084] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes. Additionally, the active ingredients are contained in an amount effective to achieve its intended purpose. Many of the compounds used in the pharmaceutical combinations disclosed herein may be provided as salts with pharmaceutically compatible counterions.

[0085] Multiple techniques of administering a compound, salt and/or composition exist in the art including, but not limited to, oral, rectal, pulmonary, topical, aerosol, injection, infusion and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections. In some embodiments, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, can be administered orally.

[0086] One may also administer the compound, salt and/or composition in a local rather than systemic manner, for example, via injection or implantation of the compound directly into the affected area, often in a depot or sustained release formulation. Furthermore, one may administer the compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken

up selectively by the organ. For example, intranasal or pulmonary delivery to target a respiratory disease or condition may be desirable.

[0087] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound and/or salt described herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Uses and Methods of Treatment

[0088] Some embodiments described herein relate to a method for ameliorating and/or treating a cancer described herein that can include administering an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) to a subject having a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for ameliorating and/or treating a cancer described herein. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound

described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) for ameliorating and/or treating a cancer described herein.

[0089] Some embodiments described herein relate to a method for inhibiting replication of a malignant growth or a tumor that can include contacting the growth or the tumor with an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof), wherein the malignant growth or tumor is due to a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for inhibiting replication of a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer described herein. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) for inhibiting replication of a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer described herein.

[0090] Some embodiments described herein relate to a method for ameliorating or treating a cancer described herein that can include contacting a malignant growth or a tumor with an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) to a subject having a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of

Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for ameliorating or treating a cancer that can include contacting a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer described herein. Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) for ameliorating or treating a cancer that can include contacting a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer described herein.

[0091] Some embodiments described herein relate to a method for inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells) that can include providing an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) to a cancer cell from a cancer described herein. Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells). Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical

composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) for inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells). Some embodiments described herein relate to a method for inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells) that can include providing an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) to a cancer cell from a cancer described herein. Other embodiments described herein relate to a method for inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells) that can include contacting a cancer cell from a cancer described herein with an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof), and thereby inhibiting the activity of WEE1.

[0092] Some embodiments described herein relate to a method for ameliorating or treating a cancer described herein that can include inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells) using an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I)

or Formula (I'), or a pharmaceutically acceptable salt thereof). Other embodiments described herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for ameliorating or treating a cancer described herein by inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells). Still other embodiments described herein relate to an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) for ameliorating or treating a cancer described herein by inhibiting the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells). Some embodiments described herein relate to a method for ameliorating or treating a cancer described herein that can include contacting a cancer cell with an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof), wherein the compound inhibits the activity of WEE1 (for example, inhibiting the activity of WEE1 in TP53-mutated cells, inhibiting the activity of WEE1 in TP53 wild-type cells, inhibiting the activity in WEE1 p53-deficient cells and/or decreasing the overexpression of WEE1 in cells).

[0093] Some embodiments disclosed herein relate to a method for inhibiting the activity of WEE1 that can include providing an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a

pharmaceutically acceptable salt thereof) to a subject having a cancer described herein or a cancer cell from a cancer described herein. Other embodiments disclosed herein relate to the use of an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for inhibiting the activity of WEE1. Still other embodiments disclosed herein relate to a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) for inhibiting the activity of WEE1.

[0094] Examples of suitable cancers include, but are not limited to: brain cancers, cervicocerebral cancers, esophageal cancers, thyroid cancers, small cell cancers, non-small cell cancers, breast cancers, lung cancers (for example non-small cell lung cancer and small cell lung cancer), stomach cancers, gallbladder/bile duct cancers, liver cancers, pancreatic cancers, colon cancers, rectal cancers, ovarian cancers, choriocarcinomas, uterus body cancers, uterocervical cancers, renal pelvis/ureter cancers, bladder cancers, prostate cancers, penis cancers, testicular cancers, fetal cancers, Wilms' cancer, skin cancers, malignant melanoma, neuroblastomas, osteosarcomas, Ewing's tumors, soft part sarcomas, acute leukemia, chronic lymphatic leukemias, chronic myelocytic leukemias, polycythemia vera, malignant lymphomas, multiple myeloma, Hodgkin's lymphomas and non-Hodgkin's lymphomas.

[0095] As described herein, a cancer can become resistant to one or more anti-cancer agents. In some embodiments, a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition that includes an effective amount of a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) can be used to treat and/or ameliorate a cancer that has become resistant to one or more anti-cancer agents (such as one or more WEE1 inhibitors). Examples of anti-cancer agents that a subject may have developed resistance to include, but are not

limited to, WEE1 inhibitors (such as AZD1775). In some embodiments, the cancer that has become resistant to one or more anti-cancer agents can be a cancer described herein.

[0096] Several known WEE1 inhibitors can cause one or more undesirable side effects in the subject being treated. Examples of undesirable side effects include, but are not limited to, thrombocytopenia, neutropenia, anemia, diarrhea, vomiting, nausea, abdominal pain, and constipation. In some embodiments, a compound described herein (for example, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof) can decrease the number and/or severity of one or more side effects associated with a known WEE1 inhibitor. In some embodiments, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, can result in a severity of a side effect (such as one of those described herein) that is 25% less than compared to the severity of the same side effect experienced by a subject receiving a known WEE1 inhibitor (such as AZD1775, formally known as MK1775 (CAS No.: 955365-80-7, 2-allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(4-(4-methylpiperazin-1-yl)phenylamino)-1,2-dihydropyrazolo[3,4-d]pyrimidin-3-one)). In some embodiments, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, results in a number of side effects that is 25% less than compared to the number of side effects experienced by a subject receiving a known WEE1 inhibitor (for example, AZD1775). In some embodiments, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, results in a severity of a side effect (such as one of those described herein) that is less in the range of about 10% to about 30% compared to the severity of the same side effect experienced by a subject receiving a known WEE1 inhibitor (such as AZD1775). In some embodiments, a compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, results in a number of side effects that is in the range of about 10% to about 30% less than compared to the number of side effects experienced by a subject receiving a known WEE1 inhibitor (for example, AZD1775).

[0097] The one or more compounds of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, that can be used to treat, ameliorate and/or inhibit the growth of a cancer wherein inhibiting the activity of WEE1 is beneficial is provided in any of the embodiments described under the heading titled "Compounds" above.

[0098] As used herein, a "subject" refers to an animal that is the object of treatment, observation or experiment. "Animal" includes cold- and warm-blooded vertebrates and invertebrates such as fish, shellfish, reptiles and, in particular, mammals. "Mammal" includes, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some embodiments, the subject can be human. In some embodiments, the subject can be a child and/or an infant, for example, a child or infant with a fever. In other embodiments, the subject can be an adult.

[0099] As used herein, the terms "treat," "treating," "treatment," "therapeutic," and "therapy" do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of the disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the subject's overall feeling of well-being or appearance.

[0100] The terms "therapeutically effective amount" and "effective amount" are used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, a therapeutically effective amount of compound, salt or composition can be the amount needed to prevent, alleviate or ameliorate symptoms of the disease or condition, or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease or condition being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0101] For example, an effective amount of a compound, or radiation, is the amount that results in: (a) the reduction, alleviation or disappearance of one or more symptoms caused by the cancer, (b) the reduction of tumor size, (c) the elimination of the tumor, and/or (d) long-term disease stabilization (growth arrest) of the tumor. In the treatment

of lung cancer (such as non-small cell lung cancer) a therapeutically effective amount is that amount that alleviates or eliminates cough, shortness of breath and/or pain. As another example, an effective amount, or a therapeutically effective amount of an WEE1 inhibitor and/or degrader is the amount which results in the reduction in WEE1 activity and/or phosphorylation (such as phosphorylation of CDC2). The reduction in WEE1 activity is known to those skilled in the art and can be determined by the analysis of WEE1 intrinsic kinase activity and downstream substrate phosphorylation.

[0102] The amount of the compound of Formula (I) or Formula (I'), or a pharmaceutically acceptable salt thereof, required for use in treatment will vary not only with the particular compound or salt selected but also with the route of administration, the nature and/or symptoms of the disease or condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician. In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the dosage ranges described herein in order to effectively and aggressively treat particularly aggressive diseases or conditions.

[0103] In general, however, a suitable dose will often be in the range of from about 0.05 mg/kg to about 10 mg/kg. For example, a suitable dose may be in the range from about 0.10 mg/kg to about 7.5 mg/kg of body weight per day, such as about 0.15 mg/kg to about 5.0 mg/kg of body weight of the recipient per day, about 0.2 mg/kg to 4.0 mg/kg of body weight of the recipient per day, or any amount in between. The compound may be administered in unit dosage form; for example, containing 1 to 500 mg, 10 to 100 mg, 5 to 50 mg or any amount in between, of active ingredient per unit dosage form.

[0104] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

[0105] As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight, the severity of the affliction, the mammalian species treated, the particular

compounds employed and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine methods, for example, human clinical trials, *in vivo* studies and *in vitro* studies. For example, useful dosages of a compound of Formula (I) or Formula (I'), or pharmaceutically acceptable salts thereof, can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Such comparison can be done by comparison against an established drug, such as cisplatin and/or gemcitabine)

[0106] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vivo* and/or *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations. Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0107] It should be noted that the attending physician would know how to and when to terminate, interrupt or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the disorder of interest will vary with the severity of the disease or condition to be treated and to the route of administration. The severity of the disease or condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0108] Compounds, salts and compositions disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be

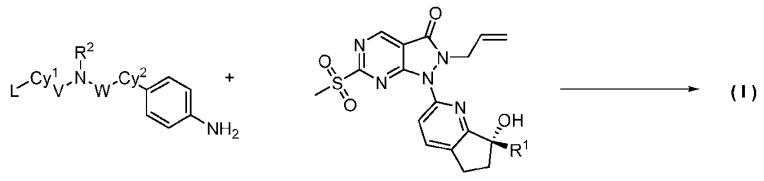
established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, dogs or monkeys, may be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, route of administration and/or regime.

EXAMPLES

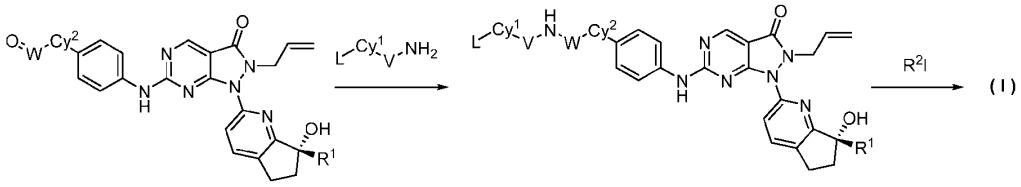
[0109] The compounds of Formula (I) or Formula (I'), and Compounds No. 1 to 36 as described herein, as well as pharmaceutically acceptable salts thereof, are prepared using General Scheme A below.

General Scheme A

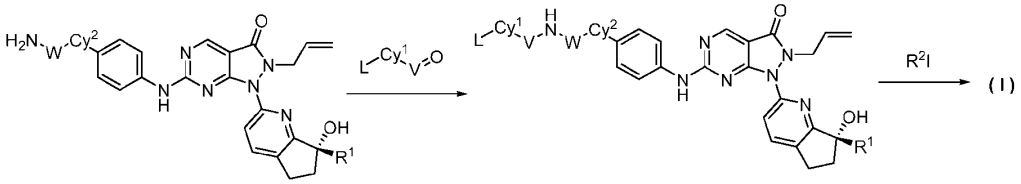
Method 1



Method 2



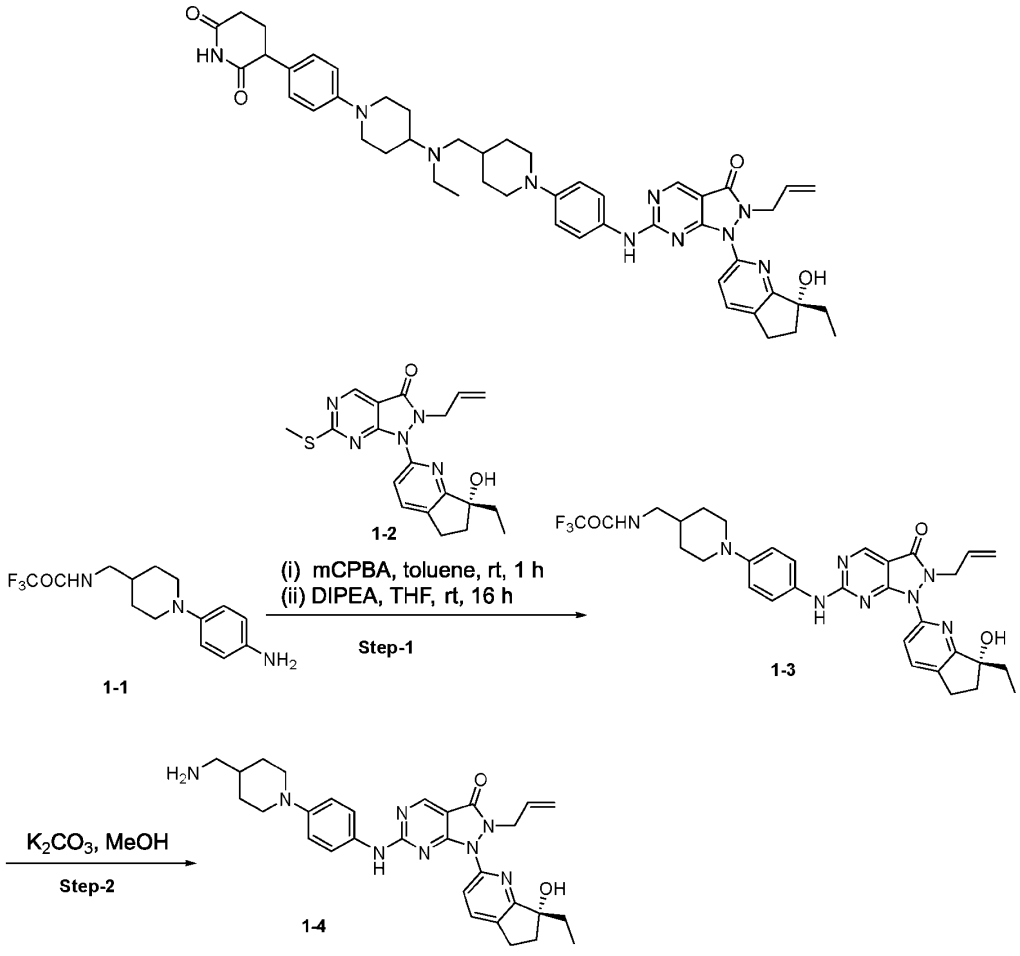
Method 3

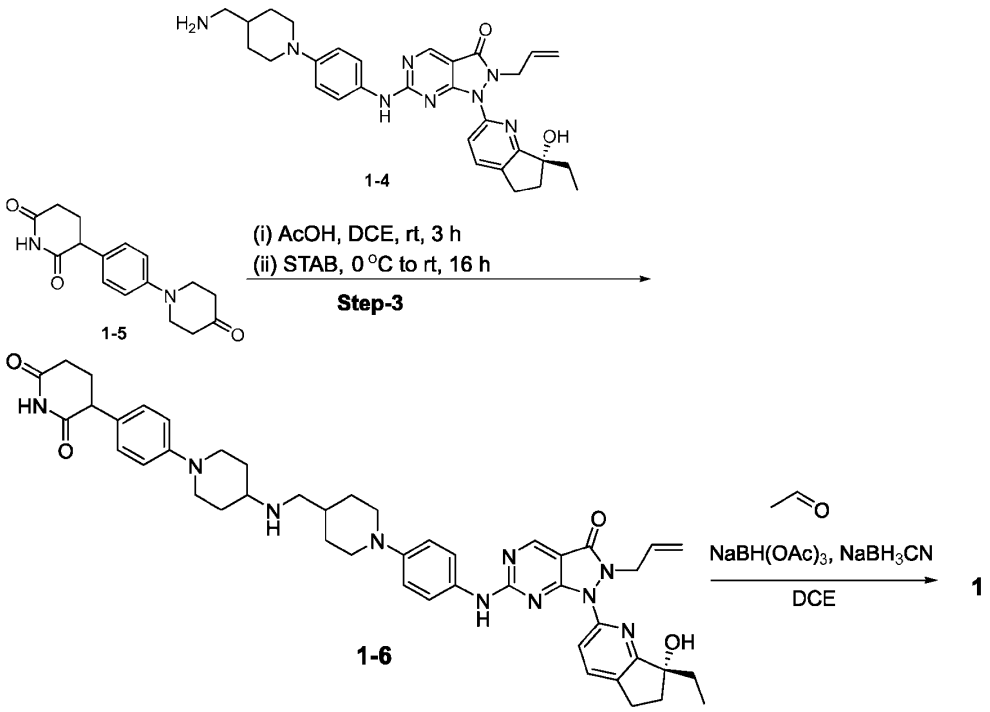


[0110] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims. Numbers in bold and within parentheses immediately ensuing a titular compound IUPAC name in each example corresponds to the Compound No. as indicated in Table 1.

Example 1

3-(4-(4-(((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(ethyl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (**1**)





[0111] Step 1: To a stirred solution of (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (5.0 g, 13.04 mmol) in toluene (100 mL), 3-chloroperoxybenzoic acid, 70-75%, (6.43 g, 26.08 mmol) was added, and the mixture stirred at room temperature (rt) for 3 h. To this mixture, a solution of *N*-((1-(4-aminophenyl)piperidin-4-yl)methyl)-2,2,2-trifluoroacetamide (3.930 g, 13.04 mmol) and *N*,*N*-diisopropylethylamine (11.40 mL, 65.19 mmol) in THF (100 mL) were added, and the mixture was stirred at rt for 16 h. The mixture was diluted with saturated $NaHCO_3$ solution (100 mL) and extracted with 10% MeOH in DCM (2 x 200 mL). The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified (silica gel flash chromatography; 0 to 3% methanol in DCM) to afford (*R*)-*N*-((1-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)-2,2,2-trifluoroacetamide (4.8 g, 58%). LC/MS (ESI) *m/z* 635.4 $[M-H]^+$.

[0112] Step 2: To a stirred solution of product from Step 1 (4.80 g, 7.539 mmol) in methanol (48 mL) at 0 °C, K_2CO_3 (2.081 g, 15.078 mmol) was added. The mixture was

stirred at rt for 16 h. The mixture was concentrated under reduced pressure. The residue was diluted with DCM (150 mL) and washed with water (2 x 50 mL). The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to get (*R*)-2-Allyl-6-((4-(4-(aminomethyl)piperidin-1-yl)phenyl)amino)-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (3.7 g, 91%). LC/MS (ESI) *m/z* 541.71 $[M+H]^+$.

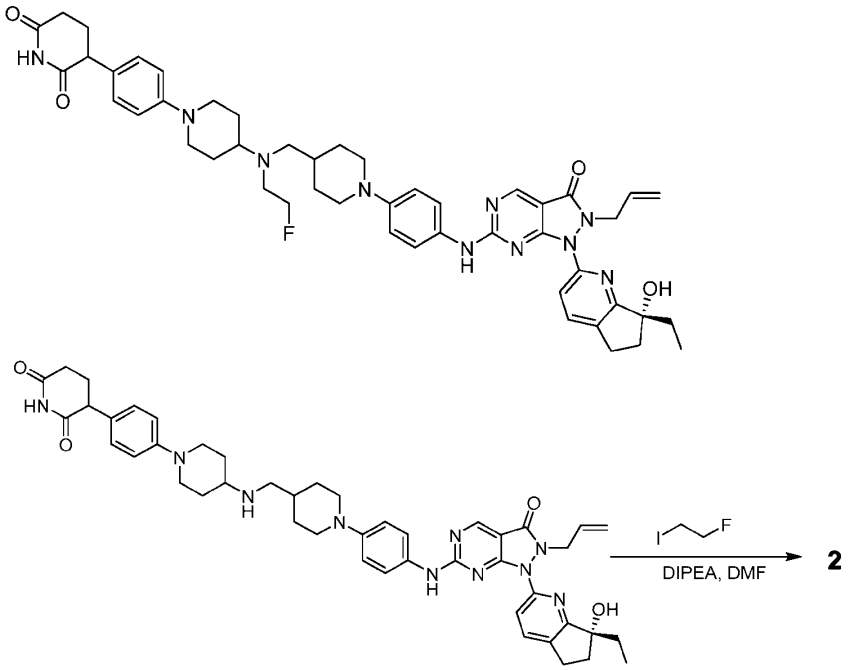
[0113] Step 3: To a stirred solution of 3-(4-(4-oxopiperidin-1-yl)phenyl)piperidine-2,6-dione (500 mg, 1.747 mmol, prepared according to WO 2023/125907 A1) and the product from Step 2 (661 mg, 1.223 mmol) in a mixture of DCE (25 mL) and acetic acid (0.11 mL), was added anhydrous NaOAc (716 mg, 8.737 mmol). The mixture was stirred at rt for 3 h. The mixture was cooled to 0 °C and sodium triacetoxy borohydride (740 mg, 3.495 mmol) was added. The resulting mixture was stirred at rt for 16 h. The reaction was quenched with water (150 mL) and extracted with 10% MeOH in dichloromethane (2 x 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford the crude product (1.1 g), which was purified (silica gel flash chromatography; 0 to 5% MeOH in DCM) to afford 3-(4-(4-(((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (513 mg, 52%). LC/MS (ESI) *m/z* 811.51 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.76 (s, 1H), 10.11 (br s, 1H), 8.81 (s, 1H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.56 (br s, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.93-6.87 (m, 4H), 5.72-5.60 (m, 1H), 5.05 (s, 1H), 5.00 (d, *J* = 9.2 Hz, 1H), 4.87 (d, *J* = 17.2 Hz, 1H), 4.80-4.70 (m, 1H), 4.60-4.50 (m, 1H), 3.75-3.68 (m, 1H), 3.66-3.55 (m, 4H), 3.01-2.95 (m, 1H), 2.75-2.52 (m, 8H), 2.50-2.40 (m, 2H), 2.21-1.98 (m, 4H), 1.95-1.80 (m, 5H), 1.73-1.68 (m, 1H), 1.60-1.48 (m, 1H), 1.40-1.18 (m, 5H), 0.87 (t, *J* = 7.2 Hz, 3H).

[0114] Step 4: To a solution of product obtained in Step 3 (50 mg, 0.062 mmol) in THF:DCM:MeOH (6:3:1, 1 mL) was added acetaldehyde (4.07 mg, 0.092 mmol) and the mixture was stirred at rt for 2 h. Sodium triacetoxyborohydride (19.60 mg, 0.092 mmol) was added and the mixture stirred at rt overnight. LCMS showed mainly starting material. Sodium cyanoborohydride (3.87 mg, 0.062 mmol) was added and the mixture stirred for 1 h. A

mixture of DCM and water was added. The organic layer was separated, dried over Na_2SO_4, concentrated and was purified (silica gel chromatography; 0-80% of 9:1, DCM: MeOH in DCM) to afford compound (**1**) (12 mg, 0.014 mmol, 23%). LC/MS (APCI) *m/z* 840.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.81-10.73 (m, 1H), 10.19-10.02 (m, 1H), 8.85-8.78 (m, 1H), 7.98-7.88 (m, 1H), 7.73-7.65 (m,1H), 7.62-7.50 (m, 2H), 7.06-6.98 (m, 2H), 6.98-6.83 (m, 4H), 5.77-5.58 (m, 1H), 5.08-4.95 (m, 2H), 4.91-4.81 (m, 1H), 4.81-4.67 (m, 1H), 4.64-4.49 (m, 1H), 3.78-3.59 (m, 5H), 3.03-2.91 (m, 1H), 2.83-2.72 (m, 1H), 2.69-2.55 (m, 6H), 2.46-2.39 (m, 1H), 2.35-1.77 (m, 10H), 1.77-1.65 (m,3H), 1.59-1.41 (m, 3H), 1.26-1.10 (m, 2H), 0.98 (s, 3H), 0.87 (s, 3H).

Example 2

3-(4-(4-(((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(2-fluoroethyl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (**2**)

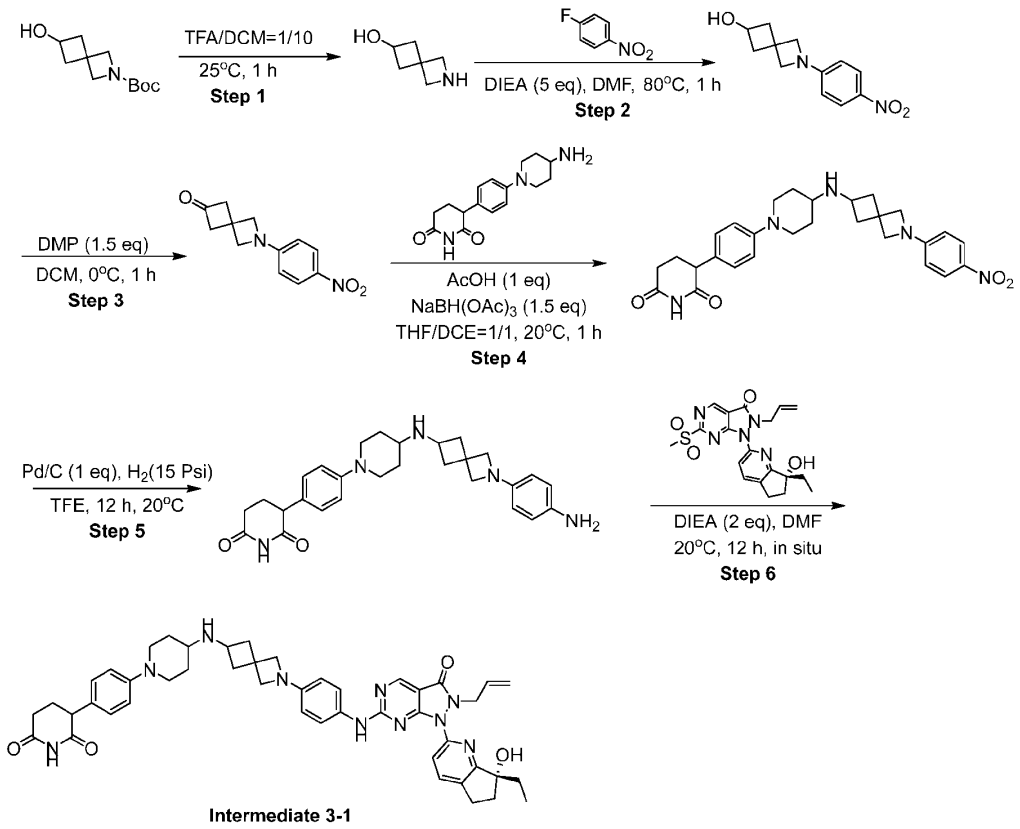


[0115] To a solution of the product obtained in Step 3 of Example 1 (50 mg, 0.062 mmol) in DMF (617 µL), was added *N,N*-diisopropylethylamine (47.8 mg, 0.370 mmol) followed by 1-fluoro-2-iodoethane (53.6 mg, 0.308 mmol). The mixture was heated at 90 °C for 8 h. The mixture was directly purified by reverse phase HPLC using 10-80% acetonitrile

(contains 0.1% formic acid) in water (contains 0.1% formic acid) to afford compound (**2**) (17 mg, 0.020 mmol, 32 %). LC/MS (APCI) *m/z* 840.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): ^1H NMR (400 MHz, DMSO-d_6): δ 10.81-10.73 (m, 1H), 10.19-10.02 (m, 1H), 8.85-8.78 (m, 1H), 7.98-7.88 (m, 1H), 7.73-7.65 (m,1H), 7.62-7.50 (m, 2H), 7.06-6.98 (m, 2H), 6.98-6.83 (m, 4H), 5.77-5.58 (m, 1H), 5.08-4.95 (m, 2H), 4.91-4.81 (m, 1H), 4.81-4.67 (m, 1H), 4.64-4.49 (m, 1H), 3.78-3.59 (m, 5H), 3.03-2.91 (m, 1H), 2.83-2.72 (m, 1H), 2.69-2.55 (m, 6H), 2.46-2.39 (m, 1H), 2.35-1.77 (m, 10H), 1.77-1.65 (m,3H), 1.59-1.41 (m, 3H), 1.26-1.10 (m, 2H), 0.98 (s, 3H), 0.87 (s, 3H).

Intermediate **3-1**

3-(4-(4-((2-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione



Intermediate **3-1**

[0116] Step 1: A solution of *tert*-butyl 6-(hydroxymethyl)-2-azaspiro[3.3]heptane-2-carboxylate (2.00 g, 8.80 mmol) in DCM (20 mL) and TFA (2 mL) was stirred at rt for 1 h. The mixture was concentrated under reduced pressure at 40 °C to give 2-azaspiro[3.3]heptan-6-ylmethanol (TFA salt) (1.10 g, yield 98%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.77 (br d, J = 2.1 Hz, 2H), 4.15 (t, J = 6.2 Hz, 4H), 3.35 (s, 4H).

[0117] Step 2: To a solution of 2-azaspiro[3.3]heptan-6-ol (1.10 g, 7.35 mmol TFA salt) in DMF (20 mL) at rt, were added 1-fluoro-4-nitro-benzene (518 mg, 3.68 mmol, 390 μL) and DIEA (2.38 g, 18.38 mmol, 3.20 mL). The mixture was stirred at 80 °C for 1 h. The mixture was diluted with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, then concentrated under reduced pressure to give 2-(4-nitrophenyl)-2-azaspiro[3.3] heptan-6-ol (0.80 g, yield 93%). LCMS (ESI): *m/z* 235.2 $[M+H]^+$, RT: 1.500 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 9.1 Hz, 2H), 6.27 (d, J = 9.1 Hz, 2H), 4.30 (quin, J = 7.0 Hz, 1H), 4.01 (d, J = 2.9 Hz, 4H), 2.65 (ddd, J = 9.9, 6.9, 2.9 Hz, 2H), 2.21 (ddd, J = 10.0, 7.2, 3.0 Hz, 2H).

[0118] Step 3: To a solution of 2-(4-nitrophenyl)-2-azaspiro[3.3]heptan-6-ol (0.80 g, 3.42 mmol) in DCM (5 mL) at 0 °C was added DMP (2.17 g, 5.12 mmol). The mixture was stirred at 0 °C for 1 h. The mixture was diluted with water (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified (silica gel chromatography; petroleum ether:ethyl acetate (50:1 to 10:1) to afford 2-(4-nitrophenyl)-2-azaspiro[3.3]heptan-6-one (0.30 g, yield 38%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09-8.03 (m, 2H), 6.53-6.43 (m, 2H), 4.25 (s, 4H), 3.40 (s, 4H).

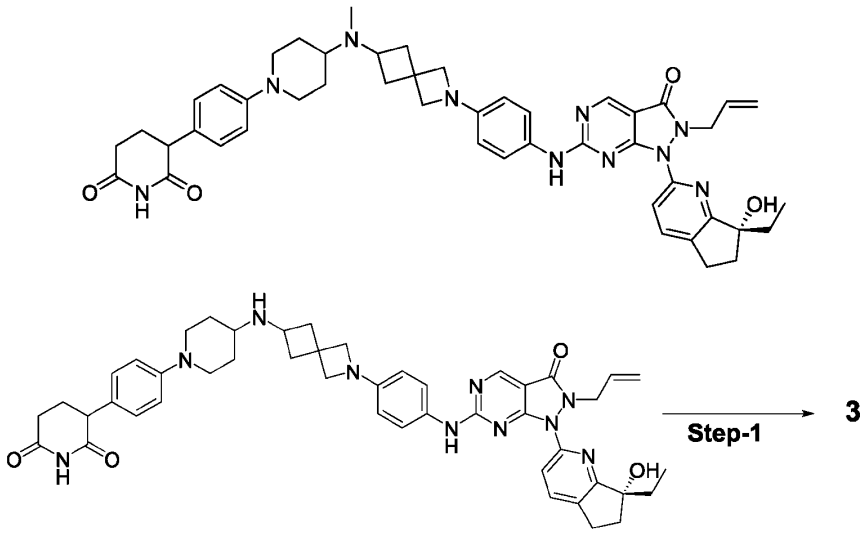
[0119] Step 4: To a mixture of 3-(4-(4-aminopiperidin-1-yl)phenyl)piperidine-2,6-dione TFA salt (777.75 mg, 1.94 mmol) in THF (2 mL) and DCE (2 mL) at rt, were added 2-(4-nitrophenyl)-2-azaspiro [3.3]heptan-6-one (0.30 g, 1.29 mmol), AcOH (77.57 mg, 1.29 mmol, 73.95 μL) and $NaBH(OAc)_3$ (410.68 mg, 1.94 mmol). The mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure at 40 °C. The crude product was purified (silica gel chromatography; petroleum ether:ethyl acetate = 100:1 to 10:1) to afford 3-(4-(4-((2-(4-nitrophenyl)-2-azaspiro[3.3]heptan-6-yl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (0.07 g, yield 11%). LCMS (ESI): *m/z* 504.3 $[M+H]^+$, RT: 1.732 min.

[0120] Step 5: To a solution of 3-(4-(4-((2-(4-nitrophenyl)-2-azaspiro[3.3]heptan-6-yl)amino)piperidin-1-yl) phenyl)piperidine-2,6-dione (0.07 g, 127.20 μmol) in THF (1 mL) under N_2, was added Pd/C (13.54 mg, 127.20 μmol). The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at rt for 12 h. The mixture was filtered and the filter cake was washed with THF (20 mL). The collected filtrate was concentrated to give 3-(4-(4-((2-(4-aminophenyl)-2-azaspiro[3.3]heptan-6-yl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (0.06 g, yield 49%, 50% purity). LCMS (ESI): *m/z* 474.3 $[M+H]^+$, RT: 0.348 min.

[0121] Step 6: To a mixture of 3-(4-(4-((2-(4-aminophenyl)-2-azaspiro[3.3]heptan-6-yl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (0.06 g, 126.02 μmol) in DMF (1 mL) at rt were added (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (52.36 mg, 126.02 μmol) and DIEA (32.57 mg, 252.04 μmol, 43.90 μL), and the mixture was stirred at rt for 12 h. The mixture was filtered and the filter was concentrated. The obtained residue was purified (Prep-HPLC; NH_4HCO_3 Condition) to afford 3-(4-(4-((2-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (50.8 mg, yield 50%). LCMS (ESI): *m/z* 809.5 $[M+H]^+$, RT: 1.997 min. ^1H NMR (400 MHz, DMSO-d_6): δ 10.95-10.61 (m, 1H), 10.23-9.86 (m, 1H), 8.79 (s, 1H), 7.88 (br d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.56-7.38 (m, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.38 (br d, *J* = 8.7 Hz, 2H), 5.74-5.58 (m, 1H), 5.04 (s, 1H), 4.99 (d, *J* = 10.0 Hz, 1H), 4.85 (br d, *J* = 16.6 Hz, 1H), 4.80-4.68 (m, 1H), 4.61-4.49 (m, 1H), 3.78 (s, 2H), 3.74-3.65 (m, 3H), 3.59 (br d, *J* = 12.3 Hz, 2H), 3.26-3.16 (m, 1H), 3.04-2.92 (m, 1H), 2.84-2.73 (m, 1H), 2.72-2.65 (m, 2H), 2.64-2.52 (m, 2H), 2.49-2.36 (m, 4H), 2.25-2.15 (m, 1H), 2.15-2.06 (m, 1H), 2.05-1.96 (m, 2H), 1.95-1.85 (m, 3H), 1.80 (br d, *J* = 9.9 Hz, 2H), 1.76-1.64 (m, 1H), 1.39-1.22 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H).

Example 3

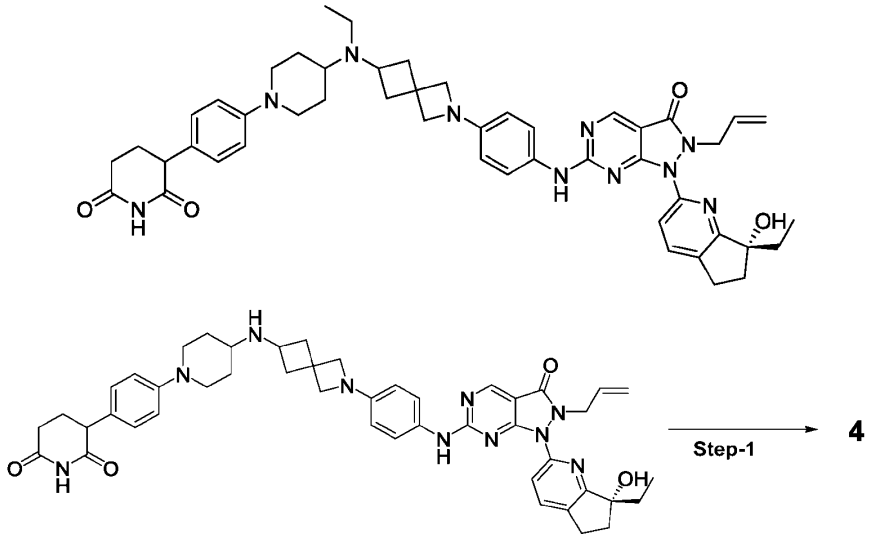
3-(4-{4-[(2-{4-[2-Allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-[1]pyrindin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamino]-phenyl}-2-aza-spiro[3.3]hept-6-yl)-methyl-amino]-piperidin-1-yl}-phenyl)-piperidine-2,6-dione (**3**)



[0122] Step 1: To a stirred solution of **Intermediate 3-1** (80 mg, 9.88 mmol and p-formaldehyde (5.9 mg, 19.77 mmol) were dissolved in dichloromethane (0.4 mL, 5 V), MeOH (0.8 mL, 10 V) and $ZnCl_2$ (16.1 mg, 11.86 mmol) were added, and the mixture stirred for 2 h at 25°C. Sodium cyanoborohydride (9.32 mg, 14.8 mmol) was added and the mixture was stirred for 16 h at 25° C. The reaction was monitored by TLC. The mixture was added to purified water (50 mL) and extracted the product by dichloromethane (2 x 300 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated to obtain a dark yellow colored crude. The crude was purified by Combiflash (8% MeOH:DCM product was eluted) to give the pure desired product (55 mg, yield 67.57%). LCMS (EI), m/z 823.7 $[M+H]^+$, ^1H NMR (300 MHz, DMSO: δ 10.77 (s, 1H), 10.15 (s, 1H), 8.79 (s, 1H), 7.87 (d, 1H, J= 8 Hz), 7.67 (d, 2H, J=8. Hz), 7.51 (s, 2H), 7.05-6.91 (m, 5H), 6.39 (s, 2H), 5.75-5.04 (m, 1H), 5.04 (s, 1H), 5.00-4.97 (m, 2H), 4.86-4.82 (m, 2H), 3.82-3.70 (m, 10H), 3.15 (s, 2H) 2.66-2.60 (m, 2H), 2.58-2.43 (m, 6H), 2.19-2.11 (m, 4H), 2.02-2.01 (m, 6H), 1.99-1.88 (m, 3H), 1.72-1.67 (m, 6H), 1.33-1.22 (m, 9H), 0.88-0.83 (m, 6H).

Example 4

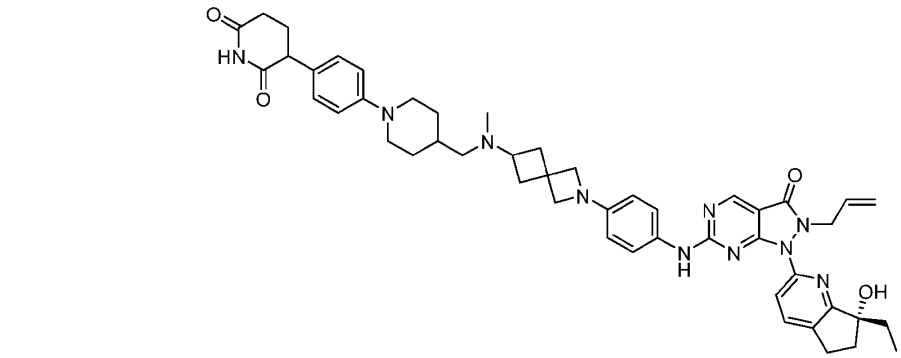
3-(4-{4-[(2-{4-[2-Allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-[1]pyrindin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamino]-phenyl}-2-aza-spiro[3.3]hept-6-yl)-ethyl-amino]-piperidin-1-yl}-phenyl)-piperidine-2,6-dione (**4**)

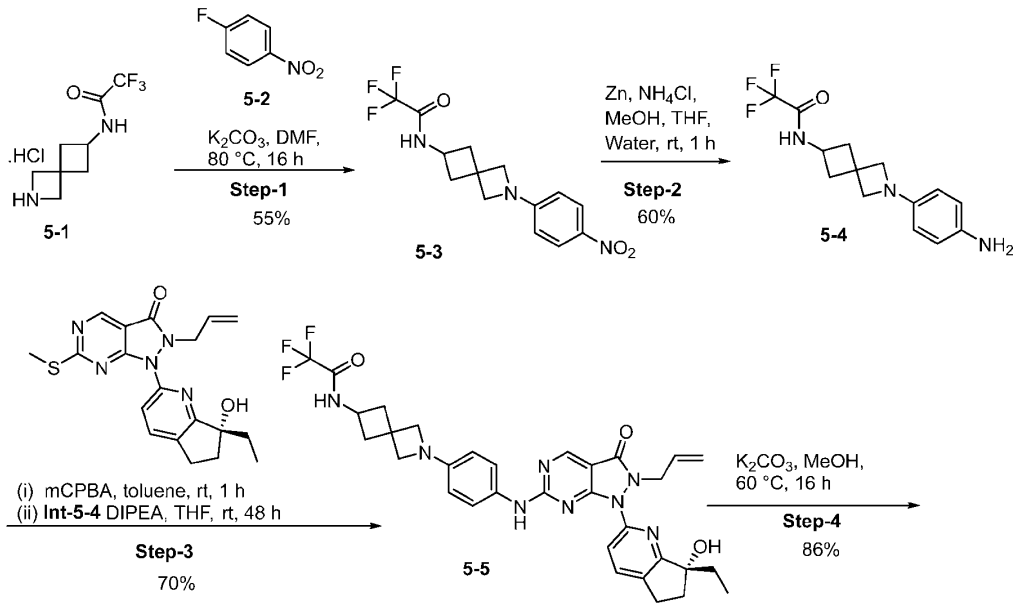


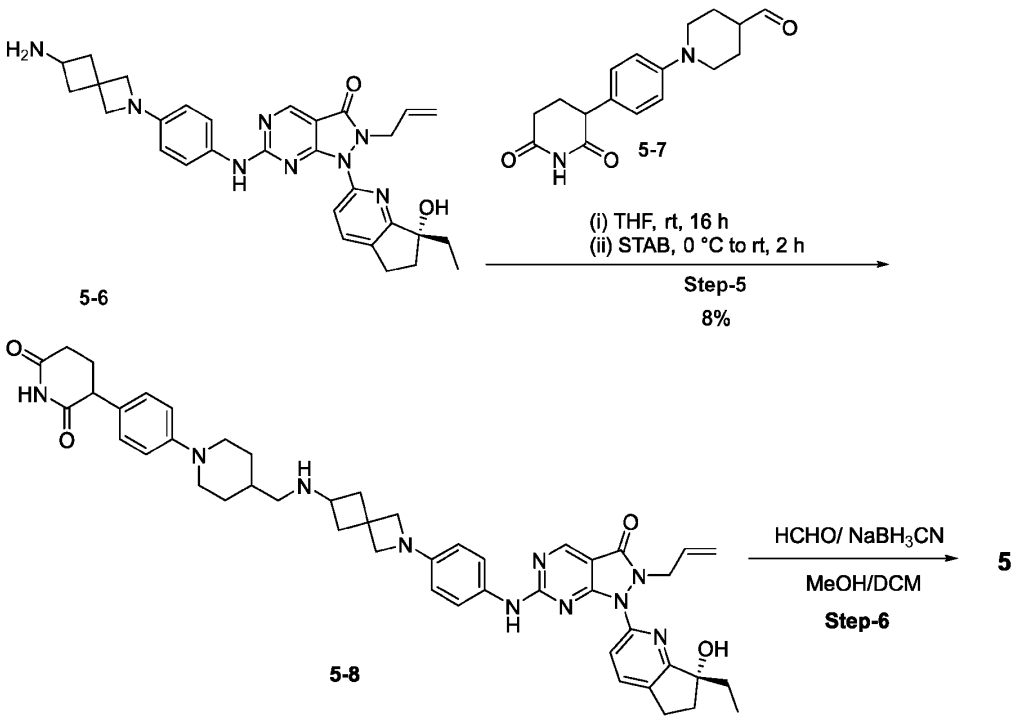
[0123] Step 1: To a stirred solution of **Intermediate 3-1** (80 mg, 9.22 mmol, and acetaldehyde (8.7 mg, 19.77 mmol) were dissolved in dichloromethane (0.4 mL, 5 V), MeOH (0.8 mL, 10 V) and $ZnCl_2$ (16.1 mg, 11.86 mmol) were added, and the mixture was stirred for 2 h at 25°C. Sodium cyanoborohydride (9.32 mg, 14.8 mmol) was added and the mixture was stirred for 16 h at 25° C. The reaction was monitored by TLC. The mixture was added to purified water (50 mL) and extracted the product by dichloromethane (2 x 300 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated to obtain a dark yellow colored crude product. The crude was purified by Combiflash (7%-8% MeOH:DCM product was eluted) to give pure desired product (57.2 mg, yield 69.16%). LCMS (EI), m/z 837.9 $[M+H]^+$, ^1H NMR (300 MHz, DMSO): δ 10.78 (s, 1H), 10.15 (s, 1H), 8.79 (s, 1H), 7.87 (d, 1H, J= 8 Hz), 7.67 (d, 2H, J=8. Hz), 7.06-7.04 (m, 2H), 6.92-6.90 (m, 5H), 6.39 (s, 2H), 5.04-5.00 (m, 1H), 4.97 (s, 1H), 5.00-4.97 (m, 2H), 4.86-4.82 (m, 2H), 3.83 (s, 3H),3.74-3.70 (m, 6H), 3.17 (m, 3H), 3.15 (s, 2H), 2.67-2.60 (m, 8H), 2.49-2.46 (m, 4H), 2.04-2.01 (m, 4H), 2.02-2.01 (m, 6H), 1.99-1.69 (m, 3H), 1.72-1.69 (m, 6H), 0.88-0.84 (m, 3H).

Example 5

3-(4-(4-(((2-(4-((2-Allyl-1-((R)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)(methyl)amino)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione (**5**)







[0124] Step 1: To a stirred solution of HCl salt of 2,2,2-trifluoro-*N*-(2-azaspiro[3.3]heptan-6-yl)acetamide (108 g, 442.3 mmol) and 1-fluoro-4-nitrobenzene (46.92 mL, 442.3 mmol) in DMF (1080 mL) at rt, K_2CO_3 (152.8 g, 1105.832 mmol) was added. The mixture was stirred at 80 °C for 16 h. After completion of the reaction, the reaction was quenched with water (2000 mL) and extracted with EtOAc (2 x 3000 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography (Eluent: 30% EtOAc in petroleum ether) to afford pure 2,2,2-trifluoro-*N*-(2-(4-nitrophenyl)-2-azaspiro[3.3]heptan-6-yl)acetamide (80 g, 55%). LC/MS (ESI) *m/z* 330.30 $[M+H]^+$.

[0125] Step 2: To a stirred solution of product obtained in Step 1 (59.9 g, 181.913 mmol) in MeOH (299.5 mL), THF (299.5 mL) and water (299.5 mL) at 0 °C, Zn dust (83.25 g, 1273.38 mmol) and NH_4Cl (68.11 g, 1273.38 mmol) were added, and the mixture was allowed to stir at rt for 1 h. After completion of the reaction, the mixture was filtered through a Buchner funnel and washed with water (1000 mL). The filtrate was extracted with EtOAc (2 x 1500 mL). The combined organic layer was dried over anhydrous

sodium sulphate, filtered and concentrated under reduced pressure to afford the crude product, which was triturated using diethyl ether (1500 mL) to afford *N*-(2-(4-aminophenyl)-2-azaspiro[3.3]heptan-6-yl)-2,2,2-trifluoroacetamide (33 g, 60%), which was directly used for next step without further purification. LC/MS (ESI) *m/z* 300.26 $[M+H]^+$.

[0126] Step 3: To a stirred solution of (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3*H*-pyrazolo[3,4-d]pyrimidin-3-one (10.25 g, 26.729 mmol) in toluene (240 mL) at 0 °C, mCPBA (70%) (13.83 g, 80.188 mmol) was added and the mixture was allowed to stir at rt for 3 h. To this mixture at rt, DIPEA (14.29 mL, 80.188 mmol) and a solution of *N*-(2-(4-aminophenyl)-2-azaspiro[3.3]heptan-6-yl)-2,2,2-trifluoroacetamide (8.0 g, 26.729 mmol) in THF (240 mL) were added and the mixture was stirred at rt for 48 h. After completion of the reaction, the reaction was quenched with water (750 mL) and extracted with EtOAc (2 x 1000 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude product, which was purified by flash chromatography (Eluent: 80% EtOAc in petroleum ether) to afford (*R*)-*N*-(2-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)-2,2,2-trifluoroacetamide (12.6 g, 70%). LC/MS (ESI) *m/z* 635.44 $[M+H]^+$.

[0127] Step 4: To a stirred solution of product obtained in Step 3 (12.5 g, 19.695 mmol) in MeOH (125 mL) at rt, K_2CO_3 (40.83 g, 295.432 mmol) was added and the mixture was stirred at 60 °C for 16 h. After completion of the reaction, the mixture was concentrated under reduced pressure. The resulting residue was taken in water (500 mL) and extracted with 10% MeOH in DCM (2 x 750 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford (*R*)-2-allyl-6-((4-(6-amino-2-azaspiro[3.3]heptan-2-yl)phenyl)amino)-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-1,2-dihydro-3*H*-pyrazolo[3,4-d]pyrimidin-3-one (8.6 g, 86%), which was directly used for next step without further purification. LC/MS (ESI) *m/z* 539.5 $[M+H]^+$.

[0128] Step 5: A solution of 1-(4-(2,6-dioxopiperidin-3-yl)phenyl)piperidine-4-carbaldehyde (6.0 g, 20.000 mmol) and the product obtained in Step 4 (10.76 g, 20.000 mmol) in THF (120 mL) was stirred at rt for 16 h. To this mixture at 0

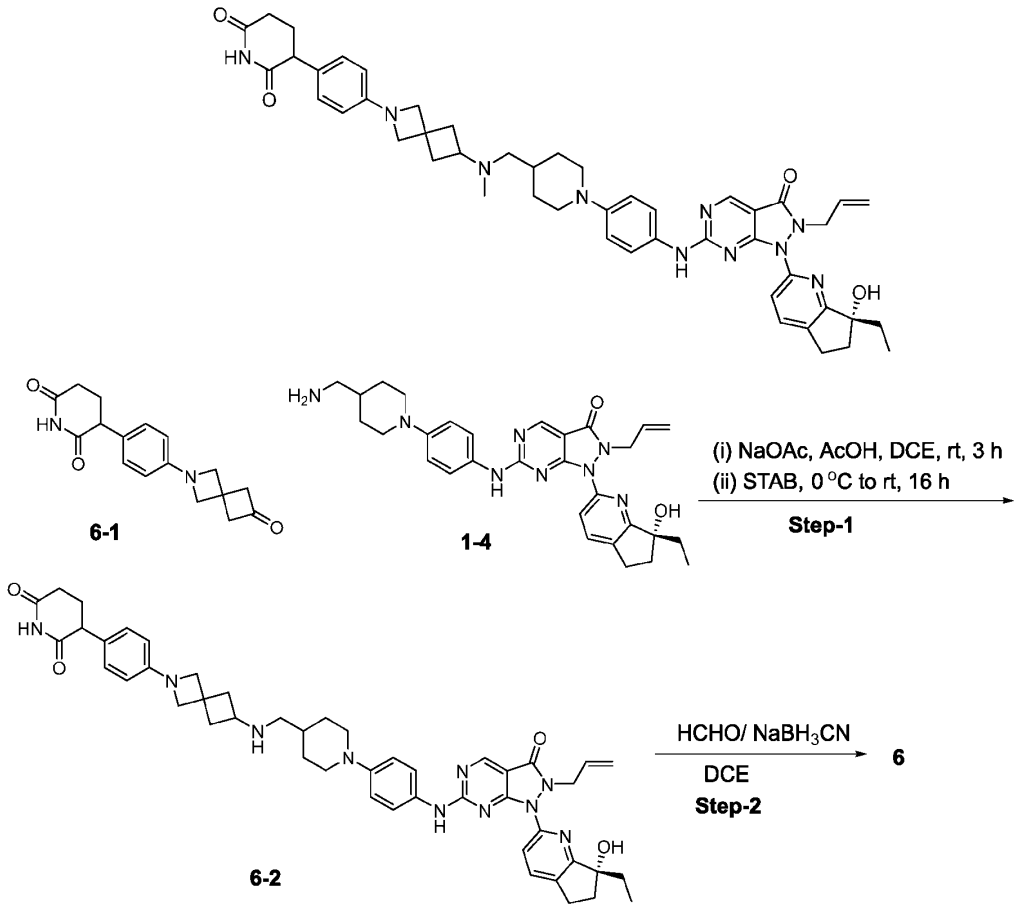
°C, STAB (8.47 g, 40.000 mmol) was added. The mixture was allowed to stir at rt for 2 h. After completion of the reaction, the reaction was quenched with water (210 mL) and extracted with 10% MeOH in DCM (4 x 300 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was re-dissolved in 10% MeOH in DCM (120 mL) and was re-precipitated out by adding EtOAc (300 mL). The resulting material was collected by filtration and dried under vacuum to afford the crude product. The crude product was purified by RP HPLC to afford pure 3-(4-(4-(((2-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)amino)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione (1.3 g, 8%). LC/MS (ESI) *m/z* 823.59 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.76 (s, 1H), 10.11 (br s, 1H), 8.79 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.50 (br s, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.39 (d, *J* = 8.8 Hz, 2H), 5.72-5.61 (m, 1H), 5.05 (s, 1H), 4.99 (d, *J* = 9.6 Hz, 1H), 4.85 (d, *J* = 12.8 Hz, 1H), 4.80-4.70 (m, 1H), 4.59-4.51 (m, 1H), 3.79-3.62 (m, 7H), 3.18-3.11 (m, 1H), 3.02-2.92 (m, 1H), 2.82-2.73 (m, 1H), 2.67-2.54 (m, 3H), 2.48-2.33 (m, 5H), 2.28-2.09 (m, 2H), 2.04-1.88 (m, 5H), 1.84-1.68 (m, 3H), 1.33 (br s, 1H), 1.26-1.18 (m, 3H), 0.87 (t, *J* = 7.2 Hz, 3H).

[0129] Step 6: To a solution of product obtained in Step 5 (90 mg, 0.109 mmol) in MeOH (1458 µl) and DCM (729 µl) was added Formalin neutral (17.75 mg, 0.219 mmol) and the mixture was stirred at rt for 1 h. The mixture was cooled to 0 °C and sodium cyanoborohydride (13.74 mg, 0.219 mmol) (in 0.2 mL THF) was added. The mixture was stirred at rt for 3 h. LCMS shows the formation of product. The product was worked up with DCM:water. The organic layer were separated, dried over Na_2SO_4, concentrated and purified by reverse phase HPLC using 10-70% acetonitrile (contains 0.1% formic acid) in water (contains 0.1% formic acid) to afford compound (**5**) (65 mg, 0.078 mmol, 71.0 % yield). LC/MS (ESI) *m/z* 837.40 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.80-10.73 (m, 1H), 10.12-9.97 (m, 1H), 8.82-8.76 (m, 1H), 8.19-8.13 (m, 1H), 7.92-7.84 (m,1H), 7.71-7.63 (m, 1H), 7.56-7.40 (m, 2H), 7.08-6.99 (m, 2H), 6.94-6.82 (m, 2H), 6.43-6.34 (m, 2H), 5.74-5.59 (m, 1H), 5.08-4.96 (m, 2H), 4.91-4.81 (m, 1H), 4.81-4.68 (m, 1H), 4.61-4.49 (m, 1H), 3.83-3.60 (m, 7H), 3.04-2.90 (m, 1H), 2.83-2.71 (m, 1H), 2.71-2.56 (m, 5H), 2.46-2.40 (m,

1H),2.35-2.07 (m, 3H), 2.07-1.83 (m, 9H), 1.83-1.52 (m, 4H), 1.24-1.08 (m, 2H), 0.91-0.83 (m, 3H).

Example 6

3-(4-(6-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(methyl)amino)-2-azaspiro[3.3]heptan-2-yl)phenyl)piperidine-2,6-dione (**6**)



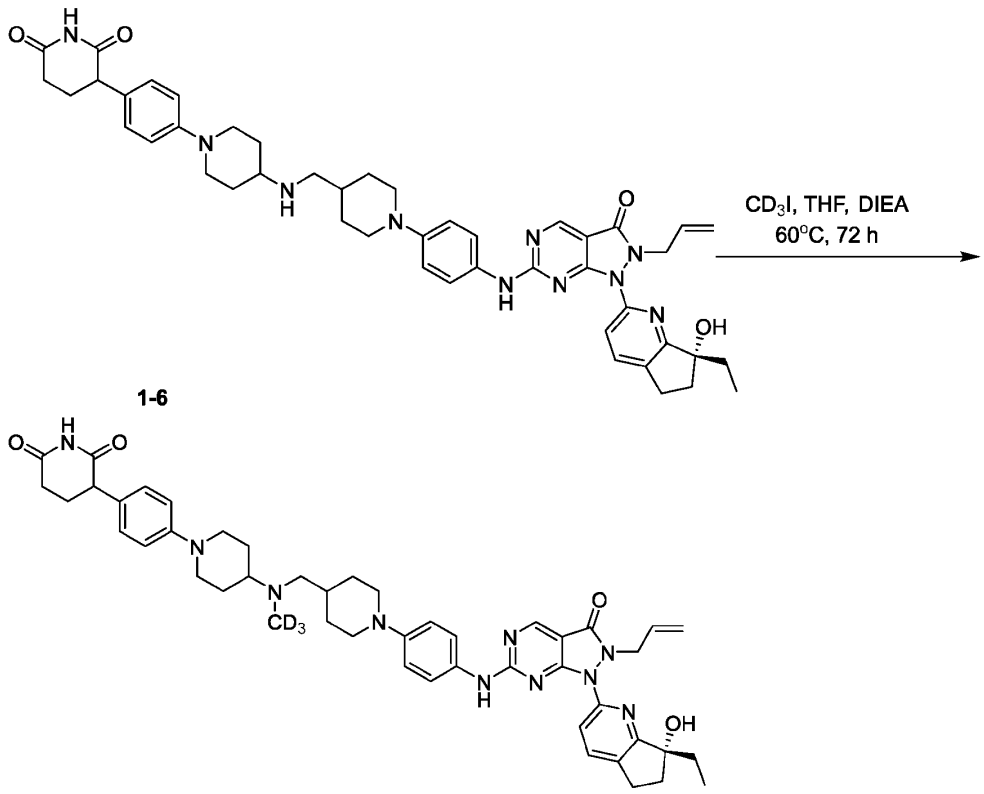
[0130] Step 1: To a stirred solution of 3-(4-(6-oxo-2-azaspiro[3.3]heptan-2-yl)phenyl)piperidine-2,6-dione (0.1 g, 0.335 mmol, WO 2023/143384 A1) and the **Intermediate 1-4** obtained from Step 2 from the synthesis of compound (**1**) (0.145 g, 0.268 mmol,) in DCE (5 mL), acetic acid (0.1 mL) and sodium acetate anhydrous (0.137 g, 1.676 mmol) were added. The mixture was stirred at rt for 3 h. To this mixture at 0 °C, sodium triacetoxy borohydride (0.142 g, 0.670 mmol) was added and the mixture was stirred at rt for

16 h. The reaction was quenched with water (25 mL) and extracted with 10% MeOH in dichloromethane (2 x 50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give a crude residue (0.15 g). The crude product was purified by RP-HPLC to afford 3-(4-(6-(((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)amino)-2-azaspiro[3.3]heptan-2-yl)phenyl)piperidine-2,6-dione (19 mg, 7%). LC/MS (APCI) *m/z* 823.52 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6): δ 10.75 (s, 1H), 10.11 (br s, 1H), 8.81 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.56 (br s, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.35 (d, *J* = 8.4 Hz, 2H), 5.72-5.62 (m, 1H), 5.05 (s, 1H), 4.99 (d, *J* = 10.0 Hz, 1H), 4.85 (d, *J* = 17.2 Hz, 1H), 4.80-4.70 (m, 1H), 4.60-4.51 (m, 1H), 3.77 (s, 2H), 3.70 (s, 2H), 3.69-3.58 (m, 3H), 3.12-3.08 (m, 1H), 3.05-2.90 (m, 1H), 2.72-2.60 (m, 1H), 2.62-2.52 (m, 3H), 2.42-2.30 (m, 4H), 2.25-2.16 (m, 1H), 2.03-1.98 (m, 2H), 1.93-1.82 (m, 6H), 1.81-1.75 (m, 2H), 1.73-1.68 (m, 1H), 1.52-1.40 (m, 1H), 1.27-1.19 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H).

[0131] Step 2: To a solution of product obtained in Step 1 (40mg, 0.049 mmol) in a mixture of DCE (1157 µl) and DCM (463 µl) was added formalin (7.89 mg, 0.097 mmol). The mixture was stirred at rt for 1 h. The mixture was cooled to 0 °C. Sodium cyanoborohydride (6.11 mg, 0.097 mmol) was added in THF (0.3 mL). The mixture was worked up with DCM:Water. The organic layer was separated, dried over Na_2SO_4, concentrated and purified by reverse phase HPLC to afford compound (**6**) (11 mg, 0.013 mmol, 27.0%). LC/MS (APCI) *m/z* 838.40 $[M+H]^+$.^{1}H NMR (400 MHz, DMSO-d_6): δ 10.78-10.68 (m, 1H), 10.19-10.00 (m, 1H), 8.85-8.77 (m, 1H), 8.00-7.84 (m,1H), 7.74-7.63 (m, 1H), 7.63-7.47 (m, 2H), 7.04-6.86 (m, 4H), 6.42-6.28 (m, 2H), 5.75-5.57 (m, 1H), 5.10-4.94 (m, 2H), 4.94-4.81 (m, 1H), 4.81-4.67 (m, 1H), 4.64-4.50 (m, 1H), 3.79 (s, 2H), 3.68 (s, 5H), 3.06-2.88 (m, 1H), 2.87-2.71 (m, 1H), 2.62 (br s, 4H), 2.48-2.37 (m, 2H), 2.34-2.06 (m, 4H), 2.06-1.98 (m, 6H), 1.97-1.66 (m, 6H), 1.66-1.48 (m, 1H), 1.29-1.11 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H).

Example 7

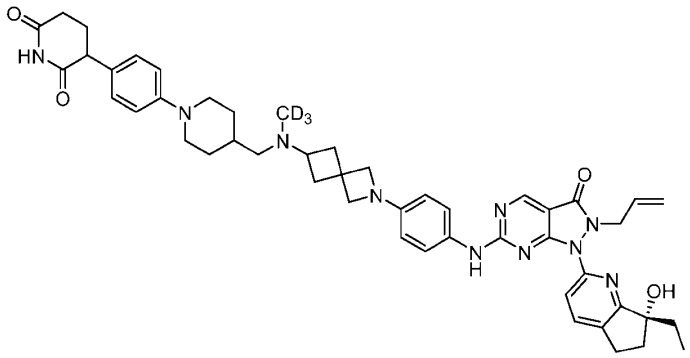
3-(4-(4-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin--yl)methyl)(methyl-d_3)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (7)



[0132] To a solution of 3-(4-(4-(((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (**Intermediate 1-6**) (52 mg, 0.064 mmol) in NMP (2 mL) were added iodomethane-d_3 (46.5 mg, 0.321 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.3 mL, 1.722 mmol). The mixture was stirred at rt for 1 h. The solvent was removed *in vacuo* and the product was purified by silica gel chromatography eluted with 0-10% MeOH in DCM. The product was further purified by reverse C18 column eluted with 0-100% MeCN/H_2O (with 0.1% formic acid). The pure product fractions were combined and saturated $NaHCO_3$ (5 mL) and EtOAc

(20 mL) were added. The organic layer was separated and aqueous was extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The product was dissolved in MeCN (1 mL) and water (1 mL). The solution was frozen and lyophilized for 2 days. 3-(4-(4-(((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (**7**) (9.4 mg, 0.011 mmol, 17.16 % yield) was obtained. LC-MS (APCI) *m/z* 828.4 [M+1]+. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.86-10.51 (m, 1H), 10.00 (s, 1H), 8.68 (s, 1H), 7.98-7.71 (m, 1H), 7.49 (br s, 3H), 7.09-6.89 (m, 2H), 6.89-6.64 (m, 5H), 5.80-5.45 (m, 1H), 5.01-4.96 (m, 1H), 4.95-4.88 (m, 1H), 4.83-4.74 (m, 1H), 4.74-4.60 (m, 1H), 4.54-4.42 (m, 1H), 3.84-3.72 (m, 1H), 3.72-3.61 (m, 2H), 3.61-3.51 (m, 2H), 2.97-2.82 (m, 1H), 2.76-2.65 (m, 1H), 2.65-2.49 (m, 5H), 2.19-1.99 (m, 3H), 1.99-1.88 (m, 2H), 1.88-1.68 (m, 4H), 1.68-1.58 (m, 1H), 1.57-1.41 (m, 2H), 1.31-1.22 (m, 4H), 1.22-1.10 (m, 3H), 0.86-0.72 (m, 3H).

Example 8
3-(4-(4-(((2-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)amino)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione (**8**)

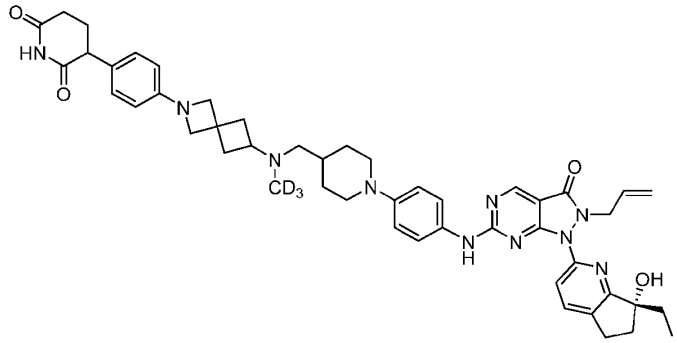


[0133] Compound **8** was synthesized from **Intermediate 5-8** following procedure of compound 7 with 46.7% yield. LC-MS (APCI) *m/z* 840.5 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.80 (s, 1H), 10.07 (s, 1H), 8.84 (s, 1H), 7.96-7.81 (m, 1H), 7.74-7.59 (m, 1H), 7.59-7.39 (m, 2H), 7.12-6.97 (m, 2H), 6.97-6.79 (m, 2H), 6.47-6.32 (m, 2H), 5.85-5.48 (m, 1H), 5.07-5.03 (m, 1H), 5.03-4.95 (m, 1H), 4.91-4.81 (m, 1H), 4.81-4.69 (m, 1H), 4.62-4.48 (m, 1H), 3.86-3.76 (m, 2H), 3.76-3.60 (m, 5H), 3.04-2.90 (m, 1H), 2.84-2.72 (m, 1H), 2.70-

2.58 (m, 4H), 2.37-2.25 (m, 2H), 2.25-2.16 (m, 1H), 2.16-2.06 (m, 1H), 2.07-1.97 (m, 4H), 1.97-1.83 (m, 3H), 1.83-1.74 (m, 2H), 1.74-1.65 (m, 1H), 1.66-1.52 (m, 1H), 1.29-1.11 (m, 3H), 0.92-0.82 (m, 3H).

Example 9

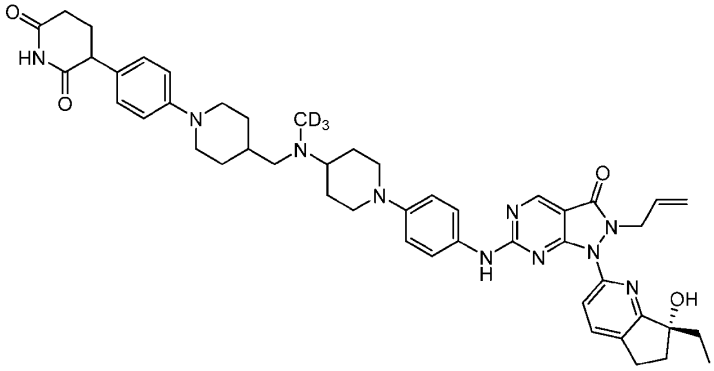
3-(4-(6-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)phenyl)piperidine-2,6-dione (**9**)

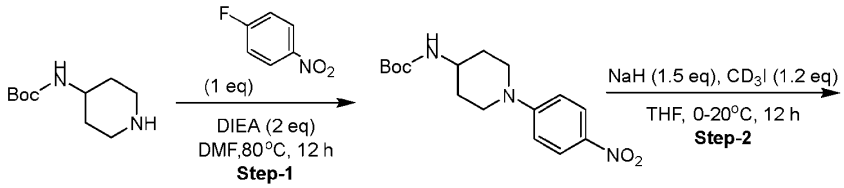


[0134] Compound **9** was synthesized from **Intermediate 6-2** following procedure of compound 7 with 40.6% yield. LC-MS (APCI) *m/z* 840.4 [M+1]+. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 1H), 10.11 (s, 1H), 8.82 (s, 1H), 8.02-7.83 (m, 1H), 7.76-7.65 (m, 1H), 7.65-7.40 (m, 2H), 7.07-6.98 (m, 2H), 6.96-6.88 (m, 2H), 6.47-6.26 (m, 2H), 5.73-5.56 (m, 1H), 5.12-5.04 (m, 1H), 5.03-4.95 (m, 1H), 4.86 (dd, *J* = 1.0, 17.1 Hz, 1H), 4.82-4.67 (m, 1H), 4.65-4.49 (m, 1H), 3.78-3.59 (m, 6H), 3.21-3.06 (m, 1H), 3.06-2.89 (m, 2H), 2.84-2.73 (m, 1H), 2.69-2.58 (m, 4H), 2.26-2.14 (m, 2H), 2.14-2.07 (m, 1H), 2.07-1.94 (m, 4H), 1.94-1.84 (m, 2H), 1.76-1.66 (m, 2H), 1.31-1.21 (m, 6H), 0.94-0.83 (m, 3H).

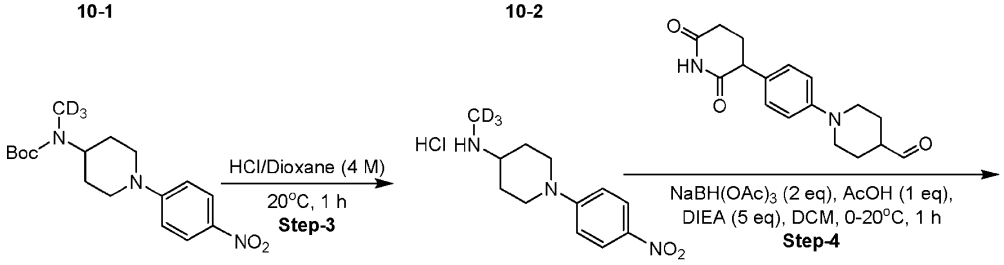
Example 10

3-(4-(4-(((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)(methyl-d_3)amino)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione (**10**)

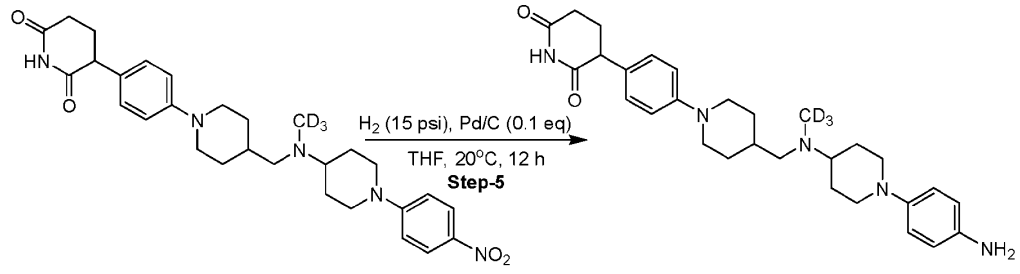




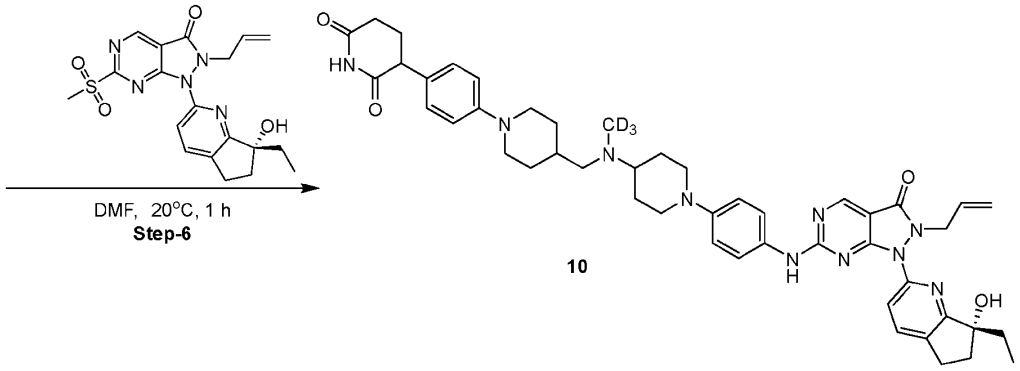
10-1 **10-2**



10-3 **10-4**



10-5 **10-6**



[0135] Step 1: To a mixture of tert-butyl piperidin-4-ylcarbamate (**10-1**) (5.00 g, 24.97 mmol) in DMF (50 mL) were added 1-fluoro-4-nitrobenzene (3.52 g, 24.97 mmol) and DIEA (6.45 g, 49.93 mmol, 8.70 mL) at 20 °C. The mixture was stirred at 80 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was poured into H_2O (50 mL) to precipitate out tert-butyl (1-(4-nitrophenyl)piperidin-4-yl) carbamate (**10-2**) (7.0 g, yield 71%, 82% purity). LCMS (ESI): *m/z* 322.2 $[M+H]^+$, RT: 1.303 min. ^1H NMR (400 MHz, DMSO-d_6): δ 8.03 (d, *J* = 9.4 Hz, 2H), 7.00 (d, *J* = 9.5 Hz, 2H), 6.89 (br d, *J* = 7.6 Hz, 1H), 3.97 (br d, *J* = 13.4 Hz, 2H), 3.64-3.49 (m, 1H), 3.17-2.99 (m, 2H), 1.80 (br d, *J* = 10.3 Hz, 2H), 1.38 (s, 10H).

[0136] Step 2: To a mixture of tert-butyl (1-(4-nitrophenyl)piperidin-4-yl)carbamate (**10-2**) (4.00 g, 10.21 mmol, 82% purity) in THF (40 mL) was added NaH (612.32 mg, 15.31 mmol, 60% purity) at 0 °C. The mixture was stirred at 20 °C for 0.5 h. To the mixture was added trideuterio(iodo)methane (1.78 g, 12.25 mmol) at 0 °C. The mixture was stirred at 2 0°C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was cooled to 0 °C and poured into NH_4Cl (20 mL). The mixture was stirred for 5 min. The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give tert-butyl (methyl-d_3)(1-(4-nitrophenyl)piperidin-4-yl)carbamate (**10-3**) (3.0 g, yield 66%, 77% purity). LCMS (ESI): *m/z* 339.2 $[M+H]^+$, RT: 1.411 min. ^1H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, *J* = 9.5 Hz, 2H), 7.03 (d, *J* = 9.5 Hz, 2H), 4.14 (br d, *J* = 13.1 Hz, 2H), 4.09-3.91 (m, 1H), 3.08-2.96 (m, 2H), 1.65 (br s, 4H), 1.39 (s, 9H).

[0137] Step 3: A mixture of tert-butyl (methyl-d_3)(1-(4-nitrophenyl)piperidin-4-yl)carbamate (**10-3**) (1.0 g, 2.28 mmol, 77% purity) in HCl:dioxane (4 M, 10 mL) was stirred at 20 °C for 1 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated in vacuum to give N-(methyl-d_3)-1-(4-nitrophenyl)piperidin-4-amine hydrochloride (**10-4**) (0.60 g, yield 86%, 90% purity, HCl salt). LCMS (ESI): *m/z* 239.2 $[M+H]^+$, RT: 0.830 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.23 (br s, 2H), 8.05 (d, *J* = 9.5 Hz, 2H), 7.06 (d, *J* = 9.5 Hz, 2H), 4.14 (br d, *J* = 13.5 Hz, 2H), 3.30-3.17 (m, 1H), 3.01 (br t, *J* = 11.9 Hz, 2H), 2.10 (br d, *J* = 10.3 Hz, 2H), 1.58 (dq, *J* = 12.0, 3.7 Hz, 2H).

[0138] Step 4: To a mixture of N-(methyl-d_3)-1-(4-nitrophenyl)piperidin-4-amine hydrochloride (**10-4**) (0.4 g, 1.50 mmol, 90% purity, HCl salt) in DCM (5 mL) were added 1-(4-(2,6-dioxopiperidin-3-yl)phenyl) piperidine-4-carbaldehyde (0.5 g, 998.83 μmol), DIEA (645.46 mg, 4.99 mmol), AcOH (59.98 mg, 998.83 μmol) and $NaBH(OAc)_3$ (423.39 mg, 2.00 mmol) at 0°C. The mixture was stirred at 20 °C for 1 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate=100:1 to 0:1)) to afford 3-(4-(4-(((methyl-d_3)(1-(4-nitrophenyl) piperidin-4-yl)amino)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione (**10-5**) (0.4 g, yield 74%, 97% purity). LCMS (ESI): *m/z* 523.2 $[M+H]^+$, RT: 1.291 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 1H), 8.02 (d, *J* = 9.4 Hz, 2H), 7.01 (dd, *J* = 5.8, 8.9 Hz, 4H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.08 (br d, *J* = 13.1 Hz, 2H), 3.71 (dd, *J* = 10.9, 4.9 Hz, 1H), 3.68-3.59 (m, 2H), 2.97 (br t, *J* = 12.0 Hz, 2H), 2.70-2.55 (m, 4H), 2.47-2.41 (m, 1H), 2.23 (br d, *J* = 7.1 Hz, 2H), 2.18-2.06 (m, 1H), 2.01 (br d, *J* = 5.0 Hz, 1H), 1.83-1.71 (m, 4H), 1.62-1.50 (m, 1H), 1.49-1.37 (m, 2H), 1.22-1.07 (m, 2H).

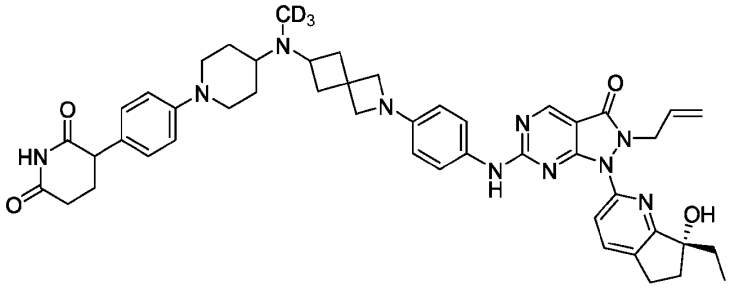
[0139] Step 5: To a solution of 3-(4-(4-(((methyl-d_3)(1-(4-nitrophenyl)piperidin-4-yl)amino)methyl) piperidin-1-yl)phenyl)piperidine-2,6-dione (**10-5**) (0.20 g, 371.18 μmol, 97% purity) in THF (5 mL) were added Pd/C (39.50 mg, 37.12 μmol, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 20 °C for 12 h. LCMS showed the reaction was completed

and the desired product was detected. The mixture was filtered through celite and the filtrate was concentrated. to afford 3-(4-(4-(((1-(4-aminophenyl)piperidin-4-yl)(methyl-d_3)amino)methyl) piperidin-1-yl)phenyl)piperidine-2,6-dione (**10-6**) (0.15 g, yield 73%, 89% purity). LCMS (ESI): *m/z* 493.3 $[M+H]^+$, RT: 0.974 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.46 (d, *J* = 8.8 Hz, 2H), 3.74-3.69 (m, 1H), 3.58 (br s, 2H), 3.37 (br d, *J* = 11.8 Hz, 2H), 2.70-2.57 (m, 3H), 2.54-2.51 (m, 1H), 2.47-2.41 (m, 2H), 2.35-2.31 (m, 1H), 2.26 (br d, *J* = 6.7 Hz, 2H), 2.17-2.07 (m, 1H), 2.05-1.95 (m, 1H), 1.83-1.67 (m, 4H), 1.61-1.46 (m, 3H), 1.23-1.09 (m, 2H).

[0140] Step 6: To a mixture of 3-(4-(4-(((1-(4-aminophenyl)piperidin-4-yl)(methyl-d_3)amino)methyl) piperidin-1-yl)phenyl)piperidine-2,6-dione (**10-6**) (0.14 g, 252.91 μmol, 89% purity) in DMF (1.5 mL) was added (R)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (105.07 mg, 252.91 μmol) at 20 °C. The mixture was stirred at 20 °C for 1 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC (NH_4HCO_3 Condition) to afford 3-(4-(4-(((1-(4-((2-allyl-1-((R)-7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)(methyl-d_3)amino)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione (**10**) (54.6 mg, yield 25%, 98% purity). LCMS (ESI): *m/z* 828.5 $[M+H]^+$, RT: 1.938 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.76 (br s, 1H), 10.10 (br s, 1H), 8.81 (s, 1H), 8.01-7.82 (m, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.55 (br d, *J* = 5.1 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.89 (br dd, *J* = 14.9, 8.9 Hz, 4H), 5.74-5.59 (m, 1H), 5.04 (s, 1H), 4.99 (d, *J* = 10.9 Hz, 1H), 4.85 (br d, *J* = 18.1 Hz, 1H), 4.80-4.70 (m, 1H), 4.63-4.49 (m, 1H), 3.78-3.59 (m, 5H), 3.03-2.90 (m, 1H), 2.85-2.72 (m, 1H), 2.61 (dt, *J* = 11.3, 5.1 Hz, 5H), 2.46-2.37 (m, 2H), 2.27 (br d, *J* = 7.0 Hz, 2H), 2.20 (s, 2H), 2.05-1.96 (m, 2H), 1.89 (br dd, *J* = 13.7, 7.5 Hz, 1H), 1.83-1.64 (m, 5H), 1.63-1.46 (m, 3H), 1.25-1.10 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

Example 11

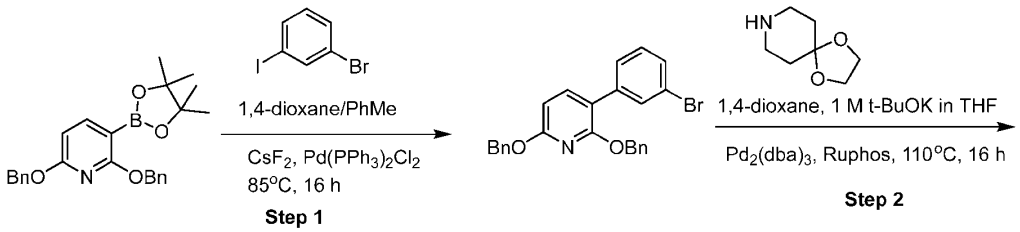
3-(4-(4-((2-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (**11**)

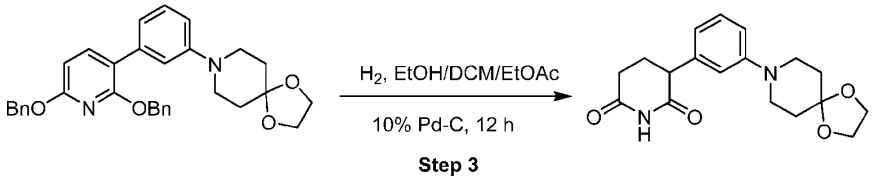


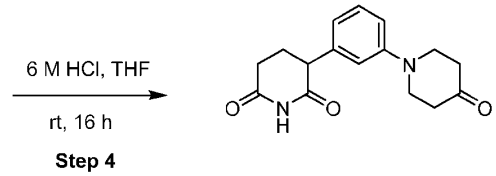
[0141] Compound **11** was synthesized from **Intermediate 3-1** following procedure of compound **7** with 47.2% yield. LC-MS (APCI) *m/z* 826.4 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.77 (s, 1H), 10.13-9.93 (m, 1H), 8.80 (s, 1H), 7.96-7.80 (m, 1H), 7.75-7.62 (m, 1H), 7.61-7.35 (m, 2H), 7.07-6.97 (m, 2H), 6.97-6.83 (m, 2H), 6.44-6.28 (m, 2H), 5.74-5.58 (m, 1H), 5.09-5.02 (m, 1H), 5.02-4.96 (m, 1H), 4.91-4.81 (m, 1H), 4.81-4.67 (m, 1H), 4.63-4.47 (m, 1H), 3.90-3.77 (m, 2H), 3.32-3.27 (m, 2H), 3.15-3.03 (m, 1H), 3.03-2.91 (m, 1H), 2.83-2.71 (m, 1H), 2.70-2.54 (m, 4H), 2.49-2.42 (m, 2H), 2.36-2.25 (m, 2H), 2.25-2.06 (m, 3H), 2.06-1.96 (m, 4H), 1.96-1.83 (m, 1H), 1.78-1.74 (m, 1H), 1.74-1.61 (m, 3H), 1.61-1.47 (m, 2H), 0.93-0.82 (m, 3H).

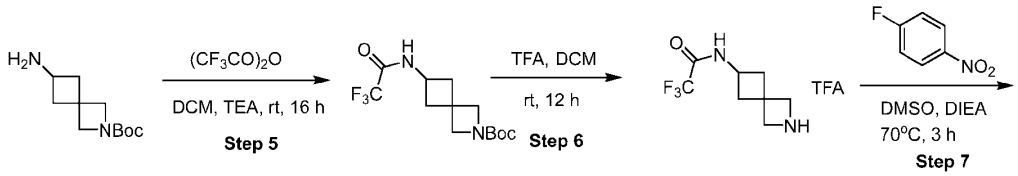
Intermediate 12-1

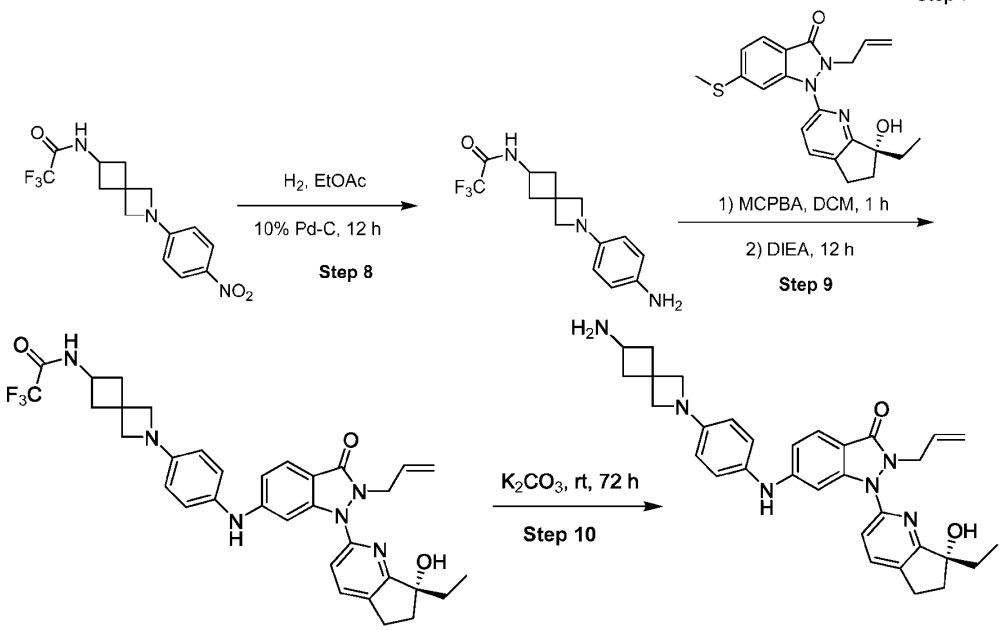
3-{3-[4-(2-{4-[2-Allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5H-[1]pyrindin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino]-phenyl}-2-aza-spiro[3.3]hept-6-ylamino)-piperidin-1-yl]-phenyl}-piperidine-2,6-dione

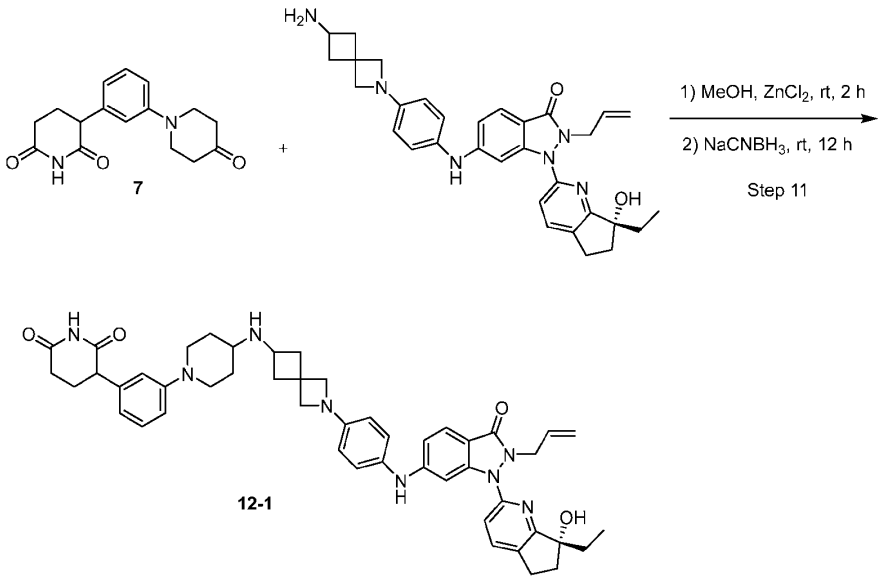



BnO
N
OBn
O
O
N
H_2, EtOH/DCM/EtOAc
10% Pd-C, 12 h
Step 3
O
N
H
O
N
O
O


6 M HCl, THF
rt, 16 h
Step 4
O
N
H
O
N
O


H_2N
NBoc
$(CF_3CO)_2O$
DCM, TEA, rt, 16 h
Step 5
O
H
N
F_3C
NBoc
TFA, DCM
rt, 12 h
Step 6
O
H
N
F_3C
NH
TFA
F
NO_2
DMSO, DIEA
70°C, 3 h
Step 7


O
H
N
F_3C
N
NO_2
H_2, EtOAc
10% Pd-C, 12 h
Step 8
O
H
N
F_3C
N
NH_2
O
N
N
S
N
OH
1) MCPBA, DCM, 1 h
2) DIEA, 12 h
Step 9
O
H
N
F_3C
N
N
H
N
N
O
N
OH
K_2CO_3, rt, 72 h
Step 10
H_2N
N
N
H
O
N
N
N
OH



[0142] Step 1: To a stirred solution of 1-bromo-3-iodobenzene (1.5 g, 5.10 mmol), 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2.80 g, 6.7 mmol), cesium fluoride (2.35 g, 15.5 mmol) was taken in 1,4-dioxane (16.5 mL, 11 V), toluene (0.99 mL, 0.66 V) and water (4.14 mL, 2.76 V). The mixture was degassed with argon for 10 min, then $Pd(pph_3)_2Cl_2$ (108 mg, 0.100 mmol) was added. The mixture was stirred for 16 h at 85 °C . Progress of the reaction was monitored by TLC. After completion of reaction, the mixture was filtered through celite bed. The filtrate was diluted with purified water and extracted with MTBE (3 x 100 mL). The combined organic layer separated, dried over sodium sulphate and concentrated under reduced pressure at 45 °C to give the crude product. The crude product was purified through column chromatography to get afford 2, 6-Bis-benzyloxy-3-(3-bromo-phenyl)-pyridine. LCMS (EI, m/z) 447.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO): δ 7.91-7.88 (1H, m), 7.49-7.45 (1H, m), 7.44-7.28 (7H, m), 6.56 (1H, d, J=8 Hz), 5.39 (2H, t, J=8.8 Hz).

[0143] Step 2: To a stirred solution of 2,6-Bis-benzyloxy-3-(3-bromo-phenyl)-pyridine (2.3 g, 5.1 mmol) in 1,4-dioxane (23 mL, 10V), 1,4-Dioxa-8-aza-spiro[4.5]decane (1.34 mL, 10.30 mmol), Ruphos (240 mg, 0.51 mmol), $Pd_2(dba)_3$ (471 mg, 0.51 mmol) and t-BuOK (1M in THF) (7.72 mL, 7.70 mmol) were added at 25-30 °C. The mixture was degassed with argon for 20 min and then stirred for 16 h at 110 °C . TLC monitored progress of the reaction. After completion of reaction, the mixture was filtered through a celite bed.

The filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified through column chromatography to get afford 8-[3-(2, 6-Bis-benzyloxy-pyridin-3-yl)-phenyl]-1, 4-dioxa-8-aza-spiro [4.5]decane. LCMS (EI, m/z) 509.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO): δ 7.91-7.88 (1H, m), 7.44-7.31 (12H, m), 7.19 (1H, t, J=8.0 Hz), 7.10 (1H, s), 6.91-6.84 (2H, m), 6.53 (1H,d, J=8.4 Hz), 5.37 (4H, d, J=11.2 Hz), 3.90 (4H, s), 3.17 (4H, t, J=10.8 Hz), 1.65 (4H, t, J=5.6 Hz).

[0144] Step 3: To a stirred solution of 8-[3-(2,6-Bis-benzyloxy-pyridin-3-yl)-phenyl]-1,4-dioxa-8-aza-spiro[4.5]decane (1.4 g, 2.90 mmol) was dissolved in EtOAc (14 mL, 10 V), ethanol (14 mL,10V) and DCM (2.8 mL,2V), 10% Pd/C(0.7g, 50%w/w) was added at 3.0 Kg/cm^2 H_2 pressure. The mixture was stirred for 12 h at 25-30 °C. Progress of the reaction was monitored by TLC. After completion of reaction, the mixture was filtered through celite. The filtrate was concentrated on rotavapor to give 3-[3-(1, 4-Dioxa-8-aza-spiro [4.5]dec-8-yl)-phenyl]-piperidine-2,6-dione (0.450 g yield, 46.5 %); LCMS (EI, m/z) 331.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO): δ 10.77 (1H, s), 7.16-7.12 (1H, m), 6.84-6.81 (2H, m), 6.59 (1H,d, J=7.6 Hz), 3.90 (4H, s), 3.77-3.73 (1H, m), 3.31-3.23 (4H, m), 2.64-2.58 (2H, m), 2.20-2.16 (1H, m), 2.14-1.98 (1H, m), 1.69 (4H, t, J=3.6 Hz).

[0145] Step 4: To a suspension of 3-[3-(1, 4-Dioxa-8-aza-spiro [4.5] dec-8-yl)-phenyl]-piperidine-2,6-dione (0.3 g, 0.908 mmol) in THF (3 mL, 10 V), 6M HCl (6 mL, 20 V) was added. The mixture stirred at 25 °C-30 °C for 16 h. The reaction was quenched with sat. sodium bicarbonate solution (pH=7-8), and then extracted with ethyl acetate (3 x 50 V). The combined organic layer dried over sodium sulphate and concentrated under reduced pressure to give the crude product. The crude product was purified by column chromatography to give 3-[3-(4-Oxo-piperidin-1-yl)-phenyl]-piperidine-2, 6-dione (0.24 g yield, 80.76%). LCMS (EI, m/z) 287.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO): δ 10.80 (1H, s), 7.20-7.16 (1H, m), 6.92-6.89 (2H, m), 6.61 (1H, d, J=7.6 Hz), 3.90-3.56 (1H, m), 3.32 (4H, s), 2.68-2.59 (1H, m), 2.23-2.17 (4H, m), 2.04 (1H, t, J=4.8 Hz), 2.01 (1H, t, J=4.8 Hz).

[0146] Step 5: To a stirred solution of tert-butyl 6-amino-2-azaspiro[3.3]heptane-2-carboxylate (1 g, 4.7083 mmol) in DCM (10 mL, 10V), was added triethylamine (1.32 mL, 9.4166 mmol) dropwise at 0-5 °C and the mixture stirred for 5 min. Trifluoroacetic acid anhydride (0.79 mL, 5.6499 mmol) was added and the mixture was stirred for 16 h at rt. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction

was quenched with saturated $NaHCO_3$ solution and extracted with DCM (3 x 100 mL). The combined organic layer was separated, dried over sodium sulphate and concentrated under reduced pressure at 45 °C to give crude product. The crude product was purified through column chromatography to afford tert-butyl 6-(2,2,2-trifluoroacetamido)-2-azaspiro[3.3]heptane-2-carboxylate (1.32 g yield, 89.65 %). ^{1}H NMR (400 MHz, DMSO): δ 9.60 (1H, d, J=7.2 Hz), 4.11 (1H, q, J=8 Hz), 3.87 (2H, s), 3.76 (2H, s), 2.49-2.44 (2H, m), 2.24-2.19 (2H, m), 1.35 (9H, s).

[0147] Step 6: To a stirred solution of tert-butyl 6-(2,2,2-trifluoroacetamido)-2-azaspiro[3.3]heptane-2-carboxylate (1.3 g, 4.21 mmol) in DCM (26 mL, 20 V), trifluoroacetic acid (6.5 mL, 5 V) were added at 0 °C. The mixture was stirred over 12 h at rt. Progress of the reaction was monitored by TLC. After completion of reaction, the mixture was concentrated on rotavapor to give the crude product. The crude product was triturated with DCM and toluene to afford 2,2,2-trifluoro-N-(2-azaspiro[3.3]heptan-6-yl)acetamide 2,2,2-trifluoroacetate. LCMS (EI, m/z) 208.18 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO): δ 11.23 (2H, s), 9.63 (1H, d, J=6.8 Hz), 8.70 (2H, s), 4.12 (1H, q, J=7.6 Hz), 3.92 (2H, s), 3.88 (2H, s), 2.59-2.49 (2H, m), 2.29-2.27 (2H, m).

[0148] Step 7: To a stirred solution of 1-fluoro-4-nitrobenzene (0.6 g, 4.2523 mmol) in DMSO (6 mL, 10V) was added DIPEA (3.7 mL, 21.2615 mmol) and 2,2,2-trifluoro-N-(2-azaspiro[3.3]heptan-6-yl)acetamide 2,2,2-trifluoroacetate (1.2 g 5.1027 mmol). The mixture was stirred for 3 h at 70 °C. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction was quenched with water and extracted with ethyl acetate (3 x 100 mL). The combined organic layer separated, dried over sodium sulphate and concentrated under reduced pressure at 45 °C to give crude product. The crude product was purified through column chromatography to give afford 2,2,2-trifluoro-N-(2-(4-nitrophenyl)-2-azaspiro[3.3]heptan-6-yl)acetamide (1.22 g yield, 87.14 %). LCMS (EI, m/z) 329.24 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO): δ: 9.63 (1H, d, J=7.2 Hz), 8.03-8.01 (2H, m), 6.42-6.39 (2H, m), 4.20 (1H, q, J=8 Hz), 4.10 (2H, s), 3.99 (2H, s), 2.61-2.56 (2H, m), 2.37-2.32 (2H, m).

[0149] Step 8: To a stirred solution of 2,2,2-trifluoro-N-(2-(4-nitrophenyl)-2-azaspiro[3.3]heptan-6-yl)acetamide (1.22 g, 3.62 mmol) in EtOAc (24 mL, 20 V) was added 10% Pd/C (1.2 g, 100%w/w) at 3.5 Kg/cm^2 H_2 pressure. The mixture was stirred for 12 h at

25-30 °C. Progress of the reaction was monitored by TLC. After completion of reaction, the mixture was filtered through a celite bed. The filtrate was concentrated on rotavapor to afford N-(2-(4-aminophenyl)-2-azaspiro[3.3]heptan-6-yl)-2,2,2-trifluoroacetamide (crude). LCMS (EI, m/z) 299.29 $[M+H]^+$. ^1H NMR (400 MHz, DMSO): δ 9.63 (1H, d, J=7.2 Hz), 8.03-8.01 (2H, m), 6.42-6.39 (2H, m), 4.20 (1H, q, J=8 Hz), 4.10 (2H, s), 3.99 (2H, s), 2.61-2.56 (2H, m), 2.37-2.32 (2H, m).

[0150] Step 9: To a stirred solution of (R)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (600 mg, 1.5646 mmol), was taken in DCM (12 mL, 20 V) and meta-chloroperbenzoic acid (0.405 g, 2.3469 mmol) was added at 0 °C to -5 °C. The mixture stirred for 1 h at the same temperature. After 1 h, N-(2-(4-aminophenyl)-2-azaspiro[3.3]heptan-6-yl)-2,2,2-trifluoroacetamide (0.491 g, 1.6428 mmol) was added to the above mixture. DIPEA (1.09 mL, 6.2586 mmol) was then added. The mixture was stirred for 12 h at rt. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction was quenched with saturated sodium sulphite solution and extracted with DCM (3 x 100 mL). The combined organic layer separated, dried over sodium sulphate and concentrated under reduced pressure at 45 °C to give the crude product. The crude product was purified through column chromatography to afford (R)-N-(2-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)-2,2,2-trifluoroacetamide (0.66 g yield, 66.46%). LCMS (EI, m/z) 634.65 $[M+H]^+$. ^1H NMR (400 MHz, DMSO): δ 10.02 (1H, s), 9.65 (1H, d, J=7.2 Hz), 8.79 (1H, s), 7.88 (1H, d, J=8 Hz), 7.67 (1H, d, J=8 Hz), 7.51 (2H, s), 6.40 (2H, d, J=8.4 Hz), 5.65 (1H, s), 5.04 (2H, s), 4.98 (2H, d, J=10.4 Hz), 4.82 (1H, s), 3.83 (2H, s), 3.72 (2H, s), 2.92 (1H, s), 2.83 (1H, s), 2.56-2.52 (2H, m), 2.33-2.28 (2H, m), 2.19 (1H, s), 1.99 (1H, d, J=9.6 Hz), 1.88 (1H, s), 1.69 (1H, d, J=6.4 Hz), 0.86 (3H, t, J=7.2 Hz).

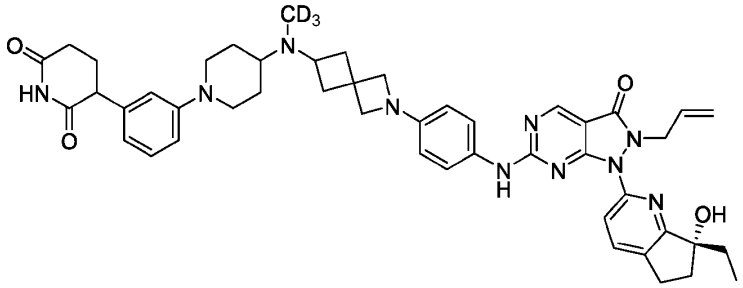
[0151] Step 10: A suspension of (R)-N-(2-(4-((2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)-2,2,2-trifluoroacetamide (0.65 g, 1.0241 mmol) in MeOH (22.75 mL, 35 V) was cooled to 0 °C-5 °C. K_2CO_3 (0.282 g, 2.0483 mmol) was added and the mixture warmed to 25 °C-30°C for 72 h. The reaction was quenched with water then extracted with 10% MeOH:DCM (3 x 30 mL). The combined organic layer was

dried over sodium sulphate and concentrated under reduced pressure. The resulting material dissolved with minimum amount of DCM (3 mL), and hexane (15 mL) was added. The solvent was decanted. The residue was concentrated under reduced pressure at 45 °C to afford (R)-2-allyl-6-((4-(6-amino-2-azaspiro[3.3]heptan-2-yl)phenyl)amino)-1-(7-ethyl-7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one. (0.502 g yield 91.10%). LCMS (EI, m/z) 538.64 $[M+H]^+$. ^1H NMR (400 MHz, DMSO): δ: 10.02 (1H, s), 8.78 (1H, s), 7.87 (1H, d, J=8.4 Hz), 7.67 (1H, d, J=8.4 Hz), 7.49 (2H, s), 6.37 (2H, d, J=8.8 Hz), 5.65 (1H, s), 5.05 (2H, s), 4.98 (2H, d, J=10.4 Hz), 4.86 (1H, s), 3.74 (2H, s), 3.66 (2H, s), 3.21 (1H, d, J=7.6 Hz), 3.18 (1H, s), 2.92 (1H, s), 2.50-2.36 (2H, m), 2.35 (1H, s), 2.19 (1H, s), 2.00-1.66 (6H, m), 1.39 (1H, s), 0.94-0.82 (5H, m).

[0152] Step 11: To a stirred solution of 2-Allyl-6-[4-(6-amino-2-aza-spiro[3.3]hept-2-yl)-phenylamino]-1-(7-ethyl-7-hydroxy-6,7-dihydro-5H-[1]pyrindin-2-yl)-1,2-dihydro-pyrazolo[3,4-d]pyrimidin-3-one (120 mg, 0.2227 mmol) and 3-[3-(4-Oxo-piperidin-1-yl)-phenyl]-piperidine-2,6-dione (76 mg, 0.2673 mmol) were dissolved in MeOH (1.2 mL, 10 V) and $ZnCl_2$ (36 mg, 0.2673 mmol) was added. The mixture was stirred for 2 h at 25 °C. Sodium cyanoborohydride (20 mg, 0.3341 mmol) was added and the mixture was stirred for 24 h at 25° C. The reaction was monitored by TLC. The mixture was added to purified water (50 mL) and extracted with 10 % MeOH:DCM (2 x 50mL). The organic layer was dried over anhydrous sodium sulphate and concentrated to obtain a dark yellow colored crude product. The crude product was purified by prep-TLC to afford 3-{3-[4-(2-{4-[2-Allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5H-[1]pyrindin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino]-phenyl}-2-aza-spiro[3.3]hept-6-ylamino)-piperidin-1-yl]-phenyl}-piperidine-2,6-dione (**12-1**) (65 mg yield, 36.11%); LCMS: (EI, m/z) 808.97 $[M+H]^+$. ^1H NMR (300 MHz, DMSO): δ: 10.02 (1H, s), 8.79 (1H, s), 7.86 (1H, s), 7.66 (1H, d, J=8.4 Hz), 7.13 (2H, s), 7.11 (1H, s), 6.81 (2H, d, J=8.4 Hz), 6.78 (2H, s), 6.57 (d, J=7.2 Hz, 1H), 6.38 (d, J=8.4Hz, 2H), 5.05-5.00 (1H, m), 5.00 (1H, bs), 4.97-4.50 (4H, m), 4.86 (1H, s), 3.79-3.60 (7H, m), 2.90-2.80 (1H, m), 2.79-2.50 (5H, m), 2.49-242 (4H, m), 2.19-2.17 (2H,m), 2.03-1.97 (8H, m), 1.84-1.81 (2H, m), 0.88-0.84 (3H,m).

Example 12

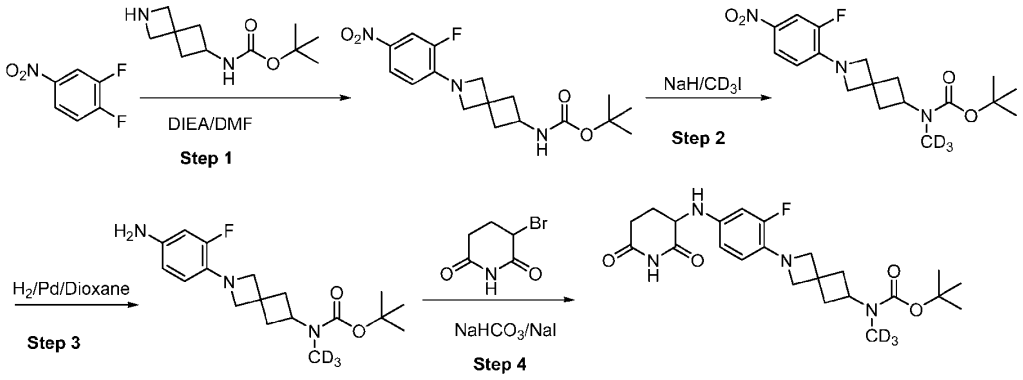
3-(3-(4-((2-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (**12**)

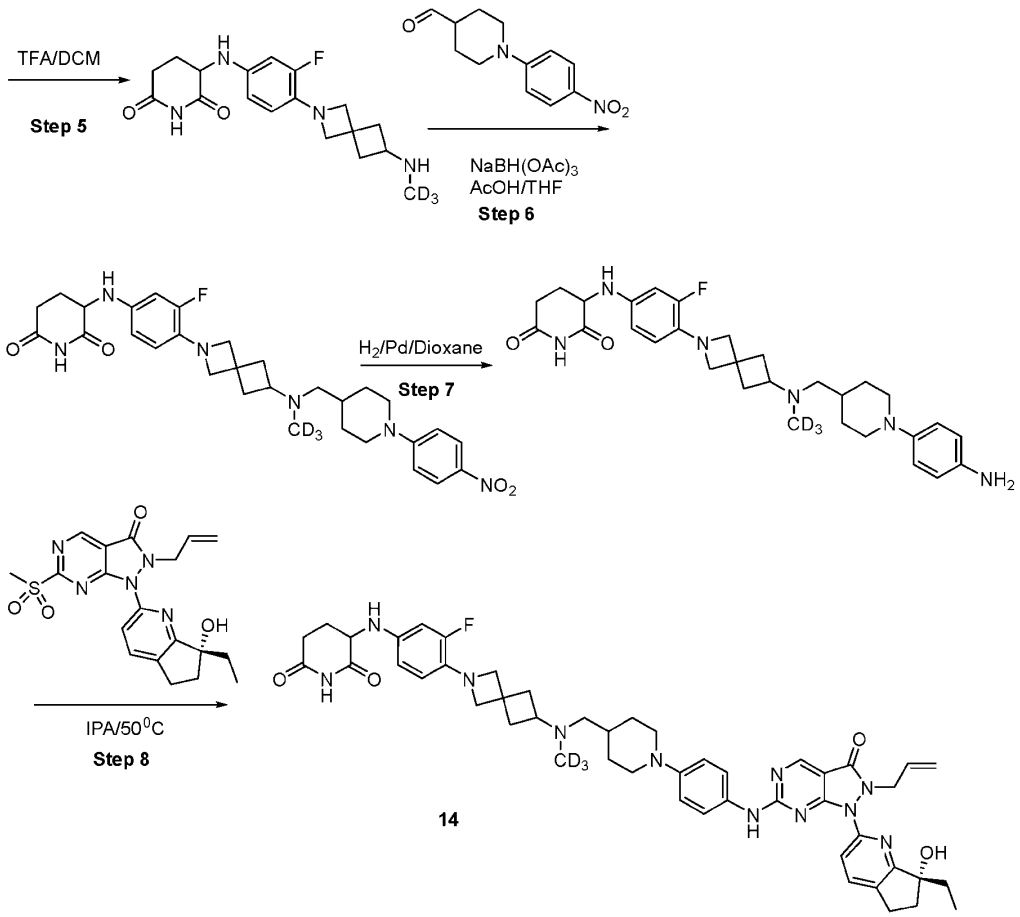


[0153] Compound **12** was synthesized from intermediate **12-1** following the procedure of compound **7** with 41.7% yield. LC-MS (APCI) *m/z* 826.4 $[M+1]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.79 (s, 1H), 10.01 (s, 1H), 8.79 (s, 1H), 7.96-7.81 (m, 1H), 7.76-7.63 (m, 1H), 7.49 (s, 2H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.86-6.72 (m, 2H), 6.64-6.49 (m, 1H), 6.39 (br d, *J* = 8.7 Hz, 2H), 5.79-5.48 (m, 1H), 5.09-5.03 (m, 1H), 5.03-4.94 (m, 1H), 4.91-4.82 (m, 1H), 4.81-4.67 (m, 1H), 4.65-4.47 (m, 1H), 3.85-3.80 (m, 2H), 3.79-3.66 (m, 5H), 3.16-3.03 (m, 1H), 3.02-2.89 (m, 1H), 2.86-2.72 (m, 1H), 2.69-2.58 (m, 4H), 2.37-2.26 (m, 2H), 2.25-2.12 (m, 3H), 2.07-1.95 (m, 4H), 1.95-1.84 (m, 1H), 1.77-1.61 (m, 3H), 1.60-1.49 (m, 2H), 0.94-0.83 (m, 3H1).

Example 13

3-((4-(6-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)-3-fluorophenyl)amino)piperidine-2,6-dione (**14**)





[0154] Step 1: To a solution of *tert*-butyl (2-azaspiro[3.3]heptan-6-yl)carbamate (3.00 g, 14.13 mmol) in DMF (30 mL) at 25 °C was added DIEA (3.65 g, 28.26 mmol, 4.92 mL) and 1,2-difluoro-4-nitrobenzene (2.25 g, 14.13 mmol, 1.56 mL). Then the reaction was stirred at 25 °C for 12 h. LCMS showed the formation of product. The reaction mixture was partitioned between ethyl acetate (200 mL) and water. The organic layer was washed with brine (200 mL) and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by column chromatography (silica gel, 0-10% ethyl acetate in petroleum ether) to afford tert-butyl (2-(2-fluoro-4-nitrophenyl)-2-azaspiro[3.3]heptan-6-yl) carbamate (4.40 g, 88%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99-7.88 (m, 1H), 7.83 (dd, J = 12.9, 2.4 Hz, 1H), 6.47 (t, J = 9.0 Hz, 1H), 4.38-4.27 (m, 1H), 4.23 (d, J = 1.8 Hz, 2H), 4.12 (d, J = 1.8 Hz, 2H), 2.51-2.35 (m, 4H), 1.46 (s, 9H).

[0155] Step 2: To a solution of *tert*-butyl (2-(2-fluoro-4-nitrophenyl)-2-azaspiro[3.3]heptan-6-yl)carbamate (4.30 g, 12.24 mmol) in THF (43 mL) at 0 °C was added NaH (734.19 mg, 18.36 mmol, 60% purity) and iodomethane-d_3 (2.66 g, 18.36 mmol, 1.14 mL). Then the reaction was stirred at 50 °C for 12 h. LCMS showed the formation of product. The residue was poured into aqueous NH_4Cl (50 mL). The aqueous phase was extracted with ethyl acetate (100 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford *tert*-butyl (2-(2-fluoro-4-nitrophenyl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)carbamate (4.50 g, 98%). ^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.99-7.88 (m, 1H), 7.83 (dd, J = 12.9, 2.4 Hz, 1H), 6.47 (t, J = 9.0 Hz, 1H), 4.38-4.27 (m, 1H), 4.23 (d, J = 1.8 Hz, 2H), 4.12 (d, J = 1.8 Hz, 2H), 2.51-2.35 (m, 4H), 1.46 (s, 9H).

[0156] Step 3: To a solution of *tert*-butyl (2-(2-fluoro-4-nitrophenyl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)carbamate (4.5 g, 12.21 mmol) in THF (80 mL) at 25 °C was added Pd/C (1.30 g, 1.22 mmol, 10% purity). The reaction was stirred at 25 °C under H_2 for 4 h. LCMS showed the reaction was completed and the desired product was detected. The reaction mixture was filtered, and the filter cake was washed with THF (80 mL), the collected filtrate was concentrated to give the crude product. The crude product was purified by trituration in PE:EA (10:1) and collected by suction filtration and dried in vacuum to afford *tert*-butyl (2-(4-amino-2-fluorophenyl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)carbamate (4.0 g, 96%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.40-6.03 (m, 3H), 4.69 (s, 2H), 3.72 (s, 2H), 3.64-3.56 (m, 3H), 2.27 (br d, J = 9.5 Hz, 4H), 1.39 (s, 9H).

[0157] Step 4: To a solution of 3-bromopiperidine-2,6-dione (3.40 g, 17.73 mmol) and *tert*-butyl (2-(4-amino-2-fluorophenyl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)carbamate (4 g, 11.82 mmol) in DMF (40 mL) at 20 °C was added $NaHCO_3$ (1.99 g, 23.64 mmol) and NaI (177.16 mg, 1.18 mmol). Then the reaction was stirred at 70 °C for 12 h. LCMS showed the formation of product. The reaction was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was washed with brine (200 mL) and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by trituration with EA:PE, 5:1 (100 mL) and collected by suction filtration and dried in vacuum to afford *tert*-butyl (2-(4-((2,6-

dioxopiperidin-3-yl)amino)-2-fluorophenyl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)carbamate (4.30 g, 81%). LC/MS (ESI) *m/z* 450.3 $[M+H]^+$.

[0158] Step 5: A solution of *tert*-butyl (2-(4-((2,6-dioxopiperidin-3-yl)amino)-2-fluorophenyl)-2-azaspiro [3.3]heptan-6-yl)(methyl-d_3)carbamate (4.3 g, 9.57 mmol) in TFA (8 mL) and DCM (40 mL) was stirred at 25 °C for 2 h. LCMS showed the formation of product. The reaction mixture was concentrated under reduced pressure at 40 °C to afford 3-((3-fluoro-4-(6-((methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)phenyl)amino)piperidine-2,6-dione (3.0 g, 90%). ^{1}H NMR (400 MHz, D_2O): δ 7.29-7.20 (m, 1H), 6.68-6.45 (m, 2H), 4.66 (s, 2H), 4.59 (s, 2H), 4.38 (br dd, *J* = 12.5, 5.1 Hz, 1H), 3.73-3.65 (m, 1H), 2.86-2.71 (m, 4H), 2.58-2.48 (m, 2H), 2.28-2.18 (m, 2H), 2.03 (dt, *J* = 12.3, 5.8 Hz, 2H).

[0159] Step 6: To a solution of 1-(4-nitrophenyl)piperidine-4-carbaldehyde (1 g, 4.27 mmol) and 3-((3-fluoro-4-(6-((methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)phenyl)amino)piperidine-2,6-dione (2.98 g, 8.54 mmol) in THF (10 mL) at 20 °C was added AcOH (25.64 mg, 426.89 μmol) and $NaBH(OAc)_3$ (1.81 g, 8.54 mmol). Then the reaction was stirred at 20 °C for 4 h. LCMS shows the formation of product. The reaction mixture was concentrated under reduced pressure at 40 °C to give the crude product. The crude product was purified by prep-HPLC to afford 3-((3-fluoro-4-(6-((methyl-d_3)((1-(4-nitrophenyl)piperidin-4-yl)methyl)amino)-2-azaspiro[3.3]heptan-2-yl)phenyl)amino)piperidine-2,6-dione (0.5 g, 21%). LC/MS (ESI) *m/z* 568.3 $[M+H]^+$.

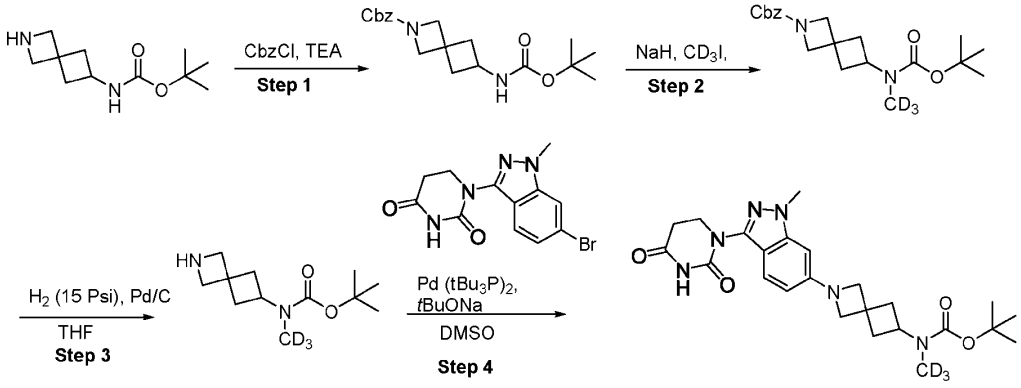
[0160] Step 7: To a solution of Pd/C (112.48 mg, 105.70 μmol, 10% purity) in dioxane (12 mL) at 25 °C was added 3-((3-fluoro-4-(6-((methyl-d_3)((1-(4-nitrophenyl)piperidin-4-yl)methyl)amino)-2-azaspiro[3.3]heptan-2-yl)phenyl)amino)piperidine-2,6-dione (0.6 g, 1.06 mmol). Then the reaction was stirred at 25 °C under H_2 (15 Psi) for 4 h. LCMS showed the reaction was completed and the desired product was detected. The reaction mixture was filtered, and the filter cake was washed with dioxane (20 mL), the collected filtrate was concentrated to afford 3-((4-(6-(((1-(4-aminophenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)-3-fluorophenyl)amino)piperidine-2,6-dione (0.53 g, 90%). LC/MS (ESI) *m/z* 537.9 $[M+H]^+$.

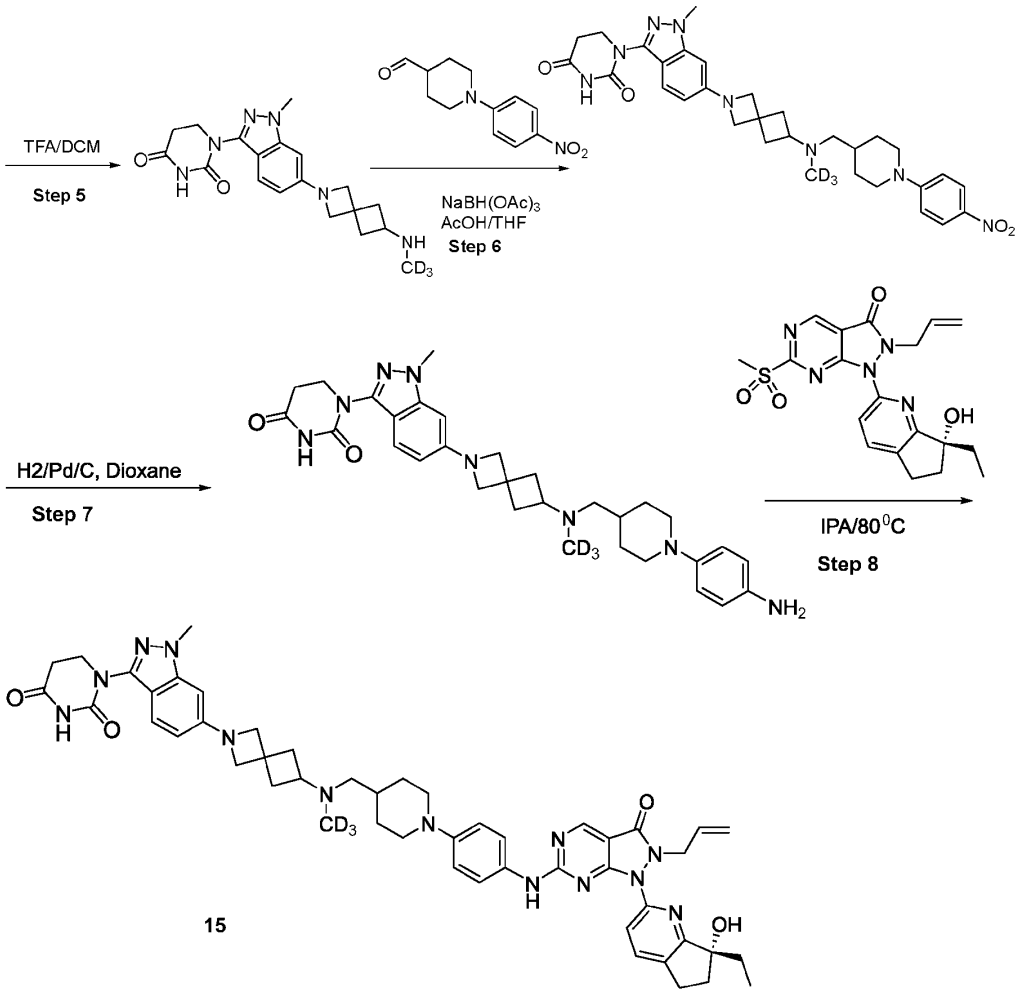
[0161] Step 8: To a solution of (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-6-(methylsulfonyl)-1,2-dihydro-3*H*-pyrazolo[3,4-d]pyrimidin-3-one (0.2 g, 481.39 μmol) IPA (2 mL) at 20 °C was added 3-((4-(6-(((1-(4-

aminophenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)-3-fluorophenyl)amino)piperidine-2,6-dione (258.84 mg, 481.39 μmol). Then the reaction mixture was stirred at 50 °C for 6 h. LCMS showed the formation of product. The reaction mixture was concentrated under reduced pressure at 40 °C to give a crude product. The crude product was purified by reverse phase HPLC to afford 3-((4-(6-(((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)-3-fluorophenyl)amino)piperidine-2,6-dione (0.049 g, 12%). LC/MS (ESI) *m/z* 873.4[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.75 (br s, 1H), 10.21-10.00 (m, 1H), 8.82 (s, 1H), 7.93 (br d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.62-7.48 (m, 2H), 6.91 (br d, *J* = 9.0 Hz, 2H), 6.47 (dd, *J* = 14.9, 2.1 Hz, 1H), 6.42-6.29 (m, 2H), 5.67 (tdd, *J* = 16.8, 10.6, 5.9 Hz, 1H), 5.53 (d, *J* = 7.4 Hz, 1H), 5.05 (s, 1H), 5.00 (d, *J* = 10.3 Hz, 1H), 4.86 (br d, *J* = 16.8 Hz, 1H), 4.76 (br dd, *J* = 10.7, 3.1 Hz, 1H), 4.57 (br dd, *J* = 16.1, 5.8 Hz, 1H), 4.18 (ddd, *J* = 11.4, 7.1, 4.8 Hz, 1H), 3.72 (s, 2H), 3.68-3.57 (m, 4H), 3.04-2.92 (m, 1H), 2.83-2.67 (m, 2H), 2.66-2.56 (m, 4H), 2.31-2.23 (m, 2H), 2.22-2.15 (m, 1H), 2.13-2.05 (m, 1H), 2.04-1.97 (m, 3H), 1.89 (br dd, *J* = 12.3, 8.3 Hz, 3H), 1.84-1.75 (m, 3H), 1.71 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.63-1.50 (m, 1H), 1.25-1.12 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H).

Example 14

(*R*)-1-((5-(6-(((1-(4-((2-Allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)methyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**15**)





[0162] Step 1: To a solution of *tert*-butyl (2-azaspiro[3.3]heptan-6-yl)carbamate (5.00 g, 23.55 mmol) in DCM (100 mL) at 0 °C were added CbzCl (4.82 g, 28.26 mmol, 4.03 mL) and TEA (4.77 g, 47.11 mmol, 6.56 mL). The reaction was stirred at 25 °C for 12 h. LCMS showed the formation of product. The reaction mixture was diluted with water (200 mL) and extracted with DCM (3 × 200 mL). The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, 0-30% ethyl acetate in petroleum ether) to afford benzyl 6-((*tert*-butoxycarbonyl)amino)-2-azaspiro[3.3]heptane-2-carboxylate (6.00 g, 70%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43-7.27 (m, 5H), 5.00 (s, 2H), 3.94 (br s, 2H),

3.82 (br s, 2H), 3.79-3.73 (m, 1H), 3.30 (s, 1H), 2.43-2.34 (m, 2H), 2.08-1.96 (m, 2H), 1.35 (s, 9H).

[0163] Step 2: To a solution of benzyl 6-((*tert*-butoxycarbonyl)amino)-2-azaspiro[3.3]heptane-2-carboxylate (6.00 g, 16.69 mmol) in THF (120 mL) at 0 °C was added NaH (1.00 g, 25.04 mmol, 60% purity) and the reaction was stirred at 0 °C for 1 h. Then iodomethane-d_3 (3.63 g, 25.04 mmol, 1.56 mL) was added to the reaction at 0 °C. The reaction was stirred at 50 °C for 11 h. LCMS shows the formation of product. The mixture was poured into aqueous NH_4Cl solution (100 mL) and the two phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give benzyl 6-((tert-butoxycarbonyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptane-2-carboxylate (6.00 g, 91%). LC/MS (ESI) *m/z* 308.3 $[M+H]^+$.

[0164] Step 3: To a solution of benzyl 6-((*tert*-butoxycarbonyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptane-2-carboxylate (6.00 g, 15.11 mmol) in 2,2,2-trifluoroethanol (120 mL) at 25 °C was added Pd/C (1.61 g, 1.51 mmol, 10% purity). Then the reaction was stirred at 25 °C under H_2 (15 Psi) for 12 h. LCMS showed the reaction was completed and the desired product was detected. The reaction mixture was filtered and the filter cake was washed with THF (200 mL), the collected filtrate was concentrated to afford *tert*-butyl(methyl-d_3)(2-azaspiro[3.3]heptan-6-yl)carbamate (4.50 g, 91%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.30-4.09 (m, 1H), 3.46 (s, 2H), 3.35 (s, 2H), 2.32-2.18 (m, 2H), 2.16-2.08 (m, 2H), 1.37 (s, 9H).

[0165] Step 4: To a solution of 1-(6-bromo-1-methyl-1H-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.5 g, 1.55 mmol) and *tert*-butyl (methyl-d_3)(2-azaspiro[3.3]heptan-6-yl) carbamate (425.81 mg, 1.86 mmol) in toluene (5 mL) was added sodium 2-methylpropan-2-olate (297.40 mg, 3.09 mmol) and palladium tri-*tert*-butylphosphane (79.07 mg, 154.73 μmol) at 25 °C. The reaction was stirred at 100 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. The reaction mixture was concentrated under reduced pressure at 25 °C and the residue obtained was purified by column chromatography (silica gel, 0-80% ethyl acetate in petroleum ether) to afford *tert*-butyl(2-(3-(2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)-1-methyl-1*H*-indazol-6-yl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)carbamate (0.54 g, 74%). ^{1}H NMR (400 MHz,

Methanol-d_4): δ 7.46 (d, J = 8.8 Hz, 1H), 6.45 (dd, J = 1.7, 8.8 Hz, 1H), 6.28 (d, J = 1.3 Hz, 1H), 4.01-3.94 (m, 4H), 3.89-3.86 (m, 4H), 2.85 (t, J = 6.7 Hz, 2H), 2.50-2.34 (m, 4H), 1.53 (s, 1H), 1.47 (s, 9H), 1.25 (d, J = 14.4 Hz, 2H).

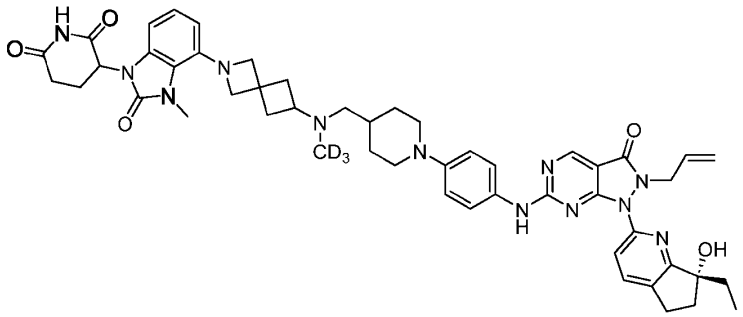
[0166] Step 5: To a solution of *tert*-butyl N-[2-[3-(2,4-dioxohexahydropyrimidin-1-yl)-1-methyl-indazol-6-yl]-2-azaspiro[3.3]heptan-6-yl]-N-(trideuteriomethyl)carbamate (320 mg, 644.66 μmol) in DCM (3 mL) was added TFA (466.64 mg, 4.09 mmol). The mixture was stirred at 25 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. All the solvents were evaporated to afford 1-[1-methyl-6-[6-(trideuteriomethylamino)-2-azaspiro[3.3]heptan-2-yl]indazol-3-yl] hexahydropyrimidine-2,4-dione (239 mg, 95%). LC/MS (ESI) m/z 372.1 $[M+H]^+$.

[0167] Step 6: To a solution of 1-(4-nitrophenyl)piperidine-4-carbaldehyde (143.19 mg, 611.25 μmol) and 1-[1-methyl-6-[6-(trideuteriomethylamino)-2-azaspiro[3.3]heptan-2-yl]indazol-3-yl]hexahydropyrimidine-2,4-dione (239 mg, 611.25 μmol) in THF (5 mL) was added AcOH (3.67 mg, 61.13 μmol). The mixture was stirred at 20 °C for 1 h. Then $NaBH(OAc)_3$ (259.10 mg, 1.22 mmol) was added to the reaction. The mixture was stirred at 20 °C for 12 h. LCMS showed the reaction was completed and the desired product was detected. All the solvents were evaporated at reduced pressure and the residue was purified by reverse phase-HPLC to afford 1-[1-methyl-6-[6-[[1-(4-nitrophenyl)-4-piperidyl]methyl-(trideuteriomethyl)amino]-2-azaspiro[3.3]heptan-2-yl]indazol-3-yl]hexahydropyrimidine-2,4-dione (290 mg, 59%). LC/MS (ESI) m/z 590.2 $[M+H]^+$.

[0168] Step 7: To a solution of 1-[1-methyl-6-[6-[[1-(4-nitrophenyl)-4-piperidyl]methyl-(trideuteriomethyl)amino]-2-azaspiro[3.3]heptan-2-yl]indazol-3-yl]hexahydropyrimidine-2,4-dione (290 mg, 467.19 μmol) in dioxane (20 mL) was added Pd/C (290 mg, 272.51 μmol, 10% purity) under N_2 atmosphere. The suspension was degassed and purged with H_2 3 times. The mixture was stirred under H_2 (15 Psi) at 50 °C for 2 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford 1-[6-[6-[[1-(4-aminophenyl)-4-piperidyl]methyl-(trideuteriomethyl)amino]-2-azaspiro[3.3]heptan-2-yl]-1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione (220 mg, 84%). LC/MS (ESI) m/z 560.5 $[M+H]^+$.

[0169] Step 8: A solution of 1-[6-[6-[[1-(4-aminophenyl)-4-piperidyl]methyl-(trideuteriomethyl)amino]-2-azaspiro[3.3]heptan-2-yl]-1-methyl-indazol-3-yl]hexahydropyrimidine-2,4-dione (190 mg, 339.46 μmol) and 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridine-2-yl]-6-methylsulfonyl-pyrazolo[3,4-d]pyrimidin-3-one (211.55 mg, 509.18 μmol) in *i*-PrOH (8 mL) was stirred at 80 °C for 5 h. LCMS showed the reaction was completed and the desired product was detected. The mixture was concentrated under reduced pressure and the residue which was purified by reverse phase-HPLC to afford 1-(6-(3-((4-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (33 mg, 11%). LC/MS (ESI) *m/z* 895.3[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 10.22-10.00 (m, 1H), 8.81 (s, 1H), 7.92 (br d, *J* = 6.6 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.56 (br s, 2H), 7.41 (d, *J* = 8.7 Hz, 1H), 6.91 (br d, *J* = 8.8 Hz, 2H), 6.33 (dd, *J* = 1.3, 8.9 Hz, 1H), 6.28 (s, 1H), 5.75-5.58 (m, 1H), 5.04 (s, 1H), 4.99 (d, *J* = 9.7 Hz, 1H), 4.85 (br d, *J* = 17.1 Hz, 1H), 4.81-4.69 (m, 1H), 4.62-4.50 (m, 1H), 3.92-3.81 (m, 7H), 3.79 (s, 2H), 3.63 (br d, *J* = 12.0 Hz, 2H), 3.04-2.91 (m, 1H), 2.83-2.57 (m, 6H), 2.32 (br s, 2H), 2.27-2.14 (m, 1H), 2.07-1.85 (m, 6H), 1.84-1.52 (m, 4H), 1.27-1.10 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H).

Example 15
3-(4-(6-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)piperidine-2,6-dione (**16**)

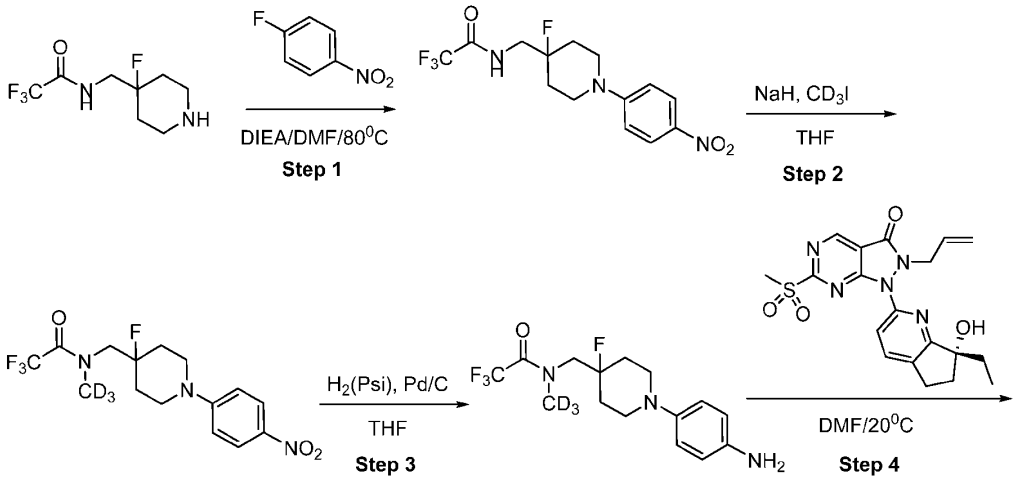


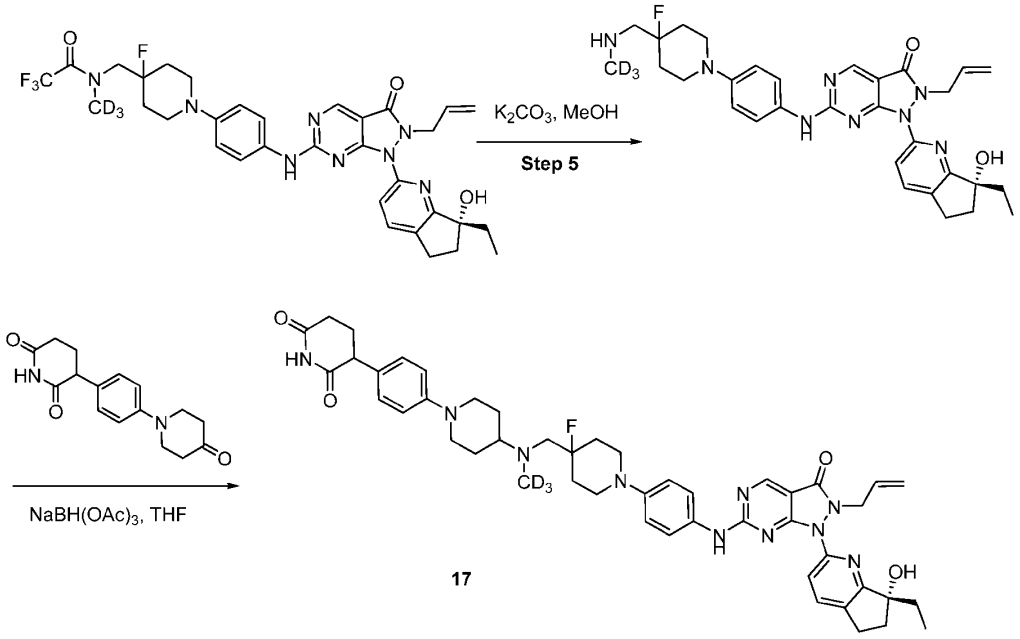
[0170] 3-(4-(6-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-

yl)amino)phenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)piperidine-2,6-dione (29% yield) was synthesized by following a similar procedure as described for the synthesis of **Example 14** using 3-(5-bromo-3-methyl-2-oxo-2,3-dihydro-1*H*-benzo[d]imidazol-1-yl)piperidine-2,6-dione instead of 1-(6-bromo-1-methyl-1*H*-indazol-3-yl)dihydropyrimidine-2,4(1*H*,3*H*)-dione. LC/MS (ESI) *m/z* 910.4 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.15-10.97 (m, 1H), 10.21-9.98 (m, 1H), 8.81 (s, 1H), 7.92 (br d, *J* = 6.9 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.64-7.44 (m, 2H), 7.00-6.85 (m, 3H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 5.74-5.60 (m, 1H), 5.31 (br dd, *J* = 12.9, 5.1 Hz, 1H), 5.09-4.96 (m, 2H), 4.85 (br d, *J* = 17.0 Hz, 1H), 4.80-4.68 (m, 1H), 4.62-4.50 (m, 1H), 3.82 (s, 2H), 3.72 (s, 2H), 3.62 (br d, *J* = 11.4 Hz, 2H), 3.56 (s, 3H), 3.02-2.92 (m, 1H), 2.91-2.81 (m, 1H), 2.81-2.70 (m, 1H), 2.69-2.64 (m, 2H), 2.62 (br s, 2H), 2.34-2.28 (m, 2H), 2.25-2.16 (m, 1H), 2.06-1.98 (m, 3H), 1.98-1.91 (m, 3H), 1.91-1.84 (m, 1H), 1.79 (br d, *J* = 10.8 Hz, 2H), 1.70 (dd, *J* = 13.5, 7.4 Hz, 1H), 1.63-1.51 (m, 1H), 1.29-1.11 (m, 3H), 0.87 (t, *J* = 7.4 Hz, 3H).

Example 16

3-(4-(4-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-4-fluoropiperidin-4-yl)methyl)(methyl-d_3)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (**17**)





[0171] Step 1: To a solution of 1-fluoro-4-nitrobenzene (667.82 mg, 4.73 mmol) in DMF (20 mL) at 25 °C were added 2,2,2-trifluoro-N-((4-fluoropiperidin-4-yl)methyl)acetamide (0.90 g, 3.94 mmol) and DIEA (2.55 g, 19.72 mmol). The reaction was stirred at 80 °C for 2 h. LCMS showed the reaction was completed and the desired product was detected. The reaction mixture was diluted with water (20 mL) and extracted with DCM (3 × 20 mL). The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 2,2,2-trifluoro-N-((4-fluoro-1-(4-nitrophenyl)piperidin-4-yl) methyl)acetamide (0.70 g, 49%). LC/MS (ESI) *m/z* 350.0 $[M+H]^+$.

[0172] Step 2: To a solution of 2,2,2-trifluoro-*N*-[[4-fluoro-1-(4-nitrophenyl)-4-piperidyl]methyl]acetamide (0.9 g, 2.58 mmol) in THF (18 mL) at 0 °C was added NaH (206.14 mg, 5.15 mmol, 60% purity,). The reaction mixture was stirred at 0 °C for 30 min. Then iodomethane-d_3 (747.04 mg, 5.15 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred for 16 h. LCMS showed the starting material was consumed completely. The reaction mixture was quenched with aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum to give a residue.

The residue was purified by prep-TLC (PE:EtOAc = 1:1) to afford 2,2,2-trifluoro-*N*-[[4-fluoro-1-(4-nitrophenyl)-4-piperidyl]methyl]-*N*-(trideuteriomethyl)acetamide (585 mg, 56%). LC/MS (ESI) *m/z* 367.3 $[M+H]^+$.

[0173] Step 3: To a suspension of Pd/C (362.55 mg, 340.68 μmol, 10% purity) in dioxane (12 mL) was added 2,2,2-trifluoro-N-[[4-fluoro-1-(4-nitrophenyl)-4-piperidyl]methyl]-N-(trideuteriomethyl) acetamide (0.65 g, 1.70 mmol) under Ar. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 Psi) at 25 °C for 12 h. LCMS showed the starting material was consumed completely. The suspension was filtered through a celite pad and the filter cake was washed with dioxane (50 mL). The filtrate was concentrated to afford *N*-[[1-(4-aminophenyl)-4-fluoro-4-piperidyl]methyl]-2,2,2-trifluoro-*N*-(trideuteriomethyl)acetamide (0.6 g, 86%). LC/MS (ESI) *m/z* 337.2 $[M+H]^+$.

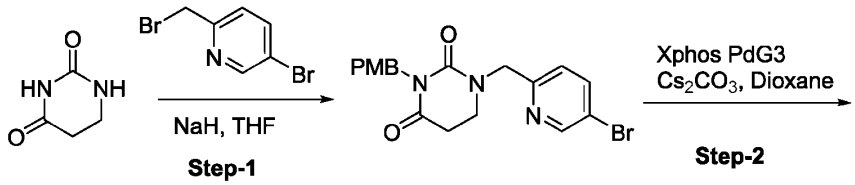
[0174] Step 4: To a solution of *N*-[[1-(4-aminophenyl)-4-fluoro-4-piperidyl]methyl]-2,2,2-trifluoro-*N*-(trideuteriomethyl)acetamide (0.55 g, 1.34 mmol) in IPA (20 mL) was added 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-6-methylsulfonyl-pyrazolo[3,4-d]pyrimidin-3-one (501.39 mg, 1.21 mmol). The reaction mixture was allowed to heat to 60 °C and stirred for 2 h. LCMS shows the formation of product. The reaction mixture was concentrated in vacuum to give a N-[[1-[4-[[2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[b]pyridin-2-yl]-3-oxo-pyrazolo[3,4-d]pyrimidin-6-yl]amino]phenyl]-4-fluoro-4-piperidyl]methyl]-2,2,2-trifluoro-N-(trideuteriomethyl)acetamide (0.825 g, 77%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.12 (br s, 1H), 8.82 (s, 1H), 8.04-7.88 (m, 1H), 7.87-7.45 (m, 3H), 7.17-6.91 (m, 2H), 5.83-5.55 (m, 1H), 5.13-4.96 (m, 2H), 4.93-4.68 (m, 2H), 4.57 (br dd, *J* = 4.9, 15.3 Hz, 1H), 3.80-3.68 (m, 2H), 3.50 (s, 1H), 3.05-2.90 (m, 3H), 2.83-2.73 (m, 1H), 2.24-2.15 (m, 1H), 2.06-1.98 (m, 1H), 1.94-1.59 (m, 7H), 0.87 (br t, *J* = 7.3 Hz, 3H).

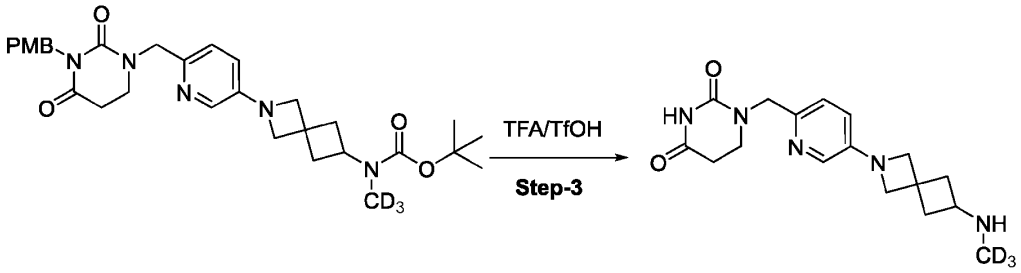
[0175] Step 5: To a solution of N-[[1-[4-[[2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*] pyridin-2-yl]-3-oxo-pyrazolo[3,4-d]pyrimidin-6-yl]amino]phenyl]-4-fluoro-4-piperidyl]methyl]-2,2,2-trifluoro-N-(trideuteriomethyl)acetamide (0.825 g, 1.23 mmol) in MeOH (25 mL) at 0 °C was added K_2CO_3 (1.70 g, 12.28 mmol). The mixture was stirred at 25 °C for 16 h. LCMS shows the formation of product. The reaction mixture was quenched with ice cold water (50 mL) and extracted with DCM (3 × 30 mL). The combined

organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated in vacuum to afford 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta [*b*]pyridin-2-yl]-6-[4-[4-fluoro-4-[(trideuteriomethylamino)methyl]-1-piperidyl]anilino]pyrazolo[3,4-d]pyrimidin-3-one (0.46 g, yield 45%). LC/MS (ESI) *m/z* 576.3 $[M+H]^+$.

[0176] Step 6: A solution of 3-[4-(4-oxo-1-piperidyl)phenyl]piperidine-2,6-dione (120 mg, 419.10 μmol) and 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[b]pyridin-2-yl]-6-[4-[4-fluoro-4-[(trideuteriomethylamino)methyl]-1-piperidyl]anilino]pyrazolo[3,4-d]pyrimidin-3-one (456.93 mg, 523.85 μmol) in THF (2 mL) was stirred at 25 °C for 0.5 h. Then $NaBH(OAc)_3$ (266.47 mg, 1.26 mmol) was added. The mixture was stirred at 25 °C for 16 h. LCMS showed the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase-HPLC to afford 3-(4-(4-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-4-fluoropiperidin-4-yl)methyl)(methyl-d_3)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione (103 mg, 29%). LC/MS (ESI) *m/z* 846.5$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 10.15 (br s, 1H), 8.82 (s, 1H), 7.93 (br d, *J* = 4.5 Hz, 1H), 7.77-7.36 (m, 3H), 7.10-6.80 (m, 6H), 5.78-5.55 (m, 1H), 5.18-4.95 (m, 2H), 4.93-4.67 (m, 2H), 4.65-4.47 (m, 1H), 3.71 (br dd, *J* = 10.8, 4.3 Hz, 3H), 3.44 (br d, *J* = 11.6 Hz, 2H), 3.03-2.87 (m, 3H), 2.81-2.73 (m, 1H), 2.61 (br dd, *J* = 17.1, 5.3 Hz, 5H), 2.48-2.44 (m, 1H), 2.25-1.63 (m, 13H), 1.61-1.42 (m, 2H), 0.87 (br t, *J* = 7.4 Hz, 3H).

Intermediate 26-1
1-((5-(6-((methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)methyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione





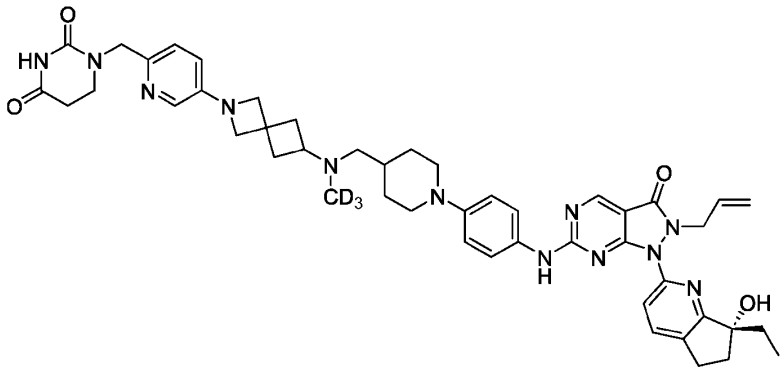
[0177] Step 1: To a solution of 3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (6 g, 25.61 mmol) in THF (60 mL) at 0 °C was added NaH (2.05 g, 51.23 mmol, 60% purity). The mixture was stirred at 0 °C for 0.5 h. A solution of 5-bromo-2-(bromomethyl)pyridine (6.43 g, 25.61 mmol) in THF (30 mL) was added to above mixture at 0 °C. The mixture was stirred at 25 °C for 4 h. LCMS showed the formation of product. The mixture was cooled to 0 °C and poured into NH_4Cl solution (100 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum to give a residue. The residue purified by column chromatography (silica gel, 10-90% ethyl acetate in petroleum ether) to afford 1-[(5-bromo-2-pyridyl)methyl]-3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (6 g, 53%). LC/MS (ESI) *m/z* 404.3 $[M+H\ ^{79}Br]^+$, 406.3 $[M+H\ ^{81}Br]^+$.

[0178] Step 2: To a mixture of 1-((5-bromopyridin-2-yl)methyl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (1.00 g, 2.47 mmol), *tert*-butyl (methyl-d_3)(2-azaspiro[3.3] heptan-6-yl)carbamate (1.13 g, 4.95 mmol), in dioxane (10 mL) at 20 °C were added XPhos Pd G3 (209.38 mg, 247.37 μmol) and Cs_2CO_3 (1.61 g, 4.95 mmol), then the reaction was stirred at 100 °C for 3 h. LCMS showed the reaction was completed and the desired product was detected. The reaction was quenched with water (30 mL) and extracted with DCM (30 mL). The combined organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, 1-100% ethyl acetate in petroleum ether) to afford *tert*-butyl (2-(6-((3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2*H*)-yl)methyl)pyridin-3-yl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)carbamate (0.70 g, 49%). LC/MS (ESI) *m/z* 553.4 $[M+H]^+$.

[0179] Step 3: A mixture of *tert*-butyl (2-(6-((3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)pyridin-3-yl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)carbamate (0.60 g, 1.09 mmol) in TFA:TfOH, 10:1, (4 mL) was stirred at 60 °C for 6 h. LCMS showed the reaction was completed and the desired product was formed. The mixture was concentrated in vacuum to afford 1-((5-(6-((methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)methyl) dihydropyrimidine-2,4(1*H*,3*H*)-dione (0.70 g, 91%) which was used to next step directly without further purification. LC/MS (ESI) *m/z* 333.1 $[M+H]^+$.

Example 17

(*R*)-1-((5-(6-(((1-(4-((2-Allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)methyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (**26**)

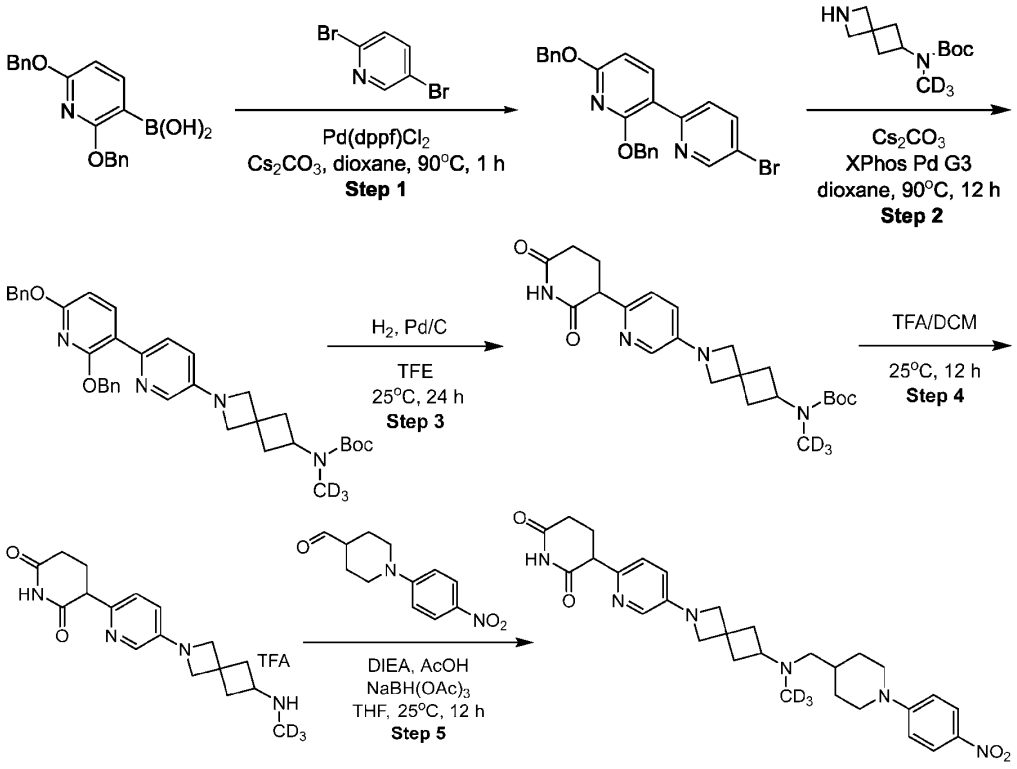


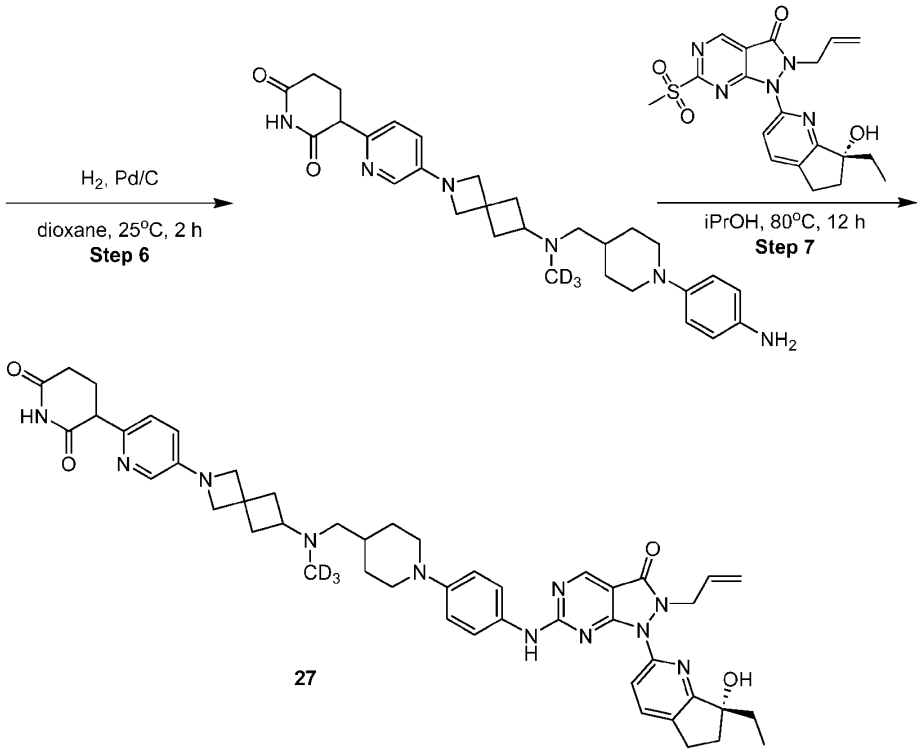
[0180] (*R*)-1-((5-(6-(((1-(4-((2-Allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)methyl)dihydropyrimidine-2,4(1*H*,3*H*)-dione (11% yield) was synthesized by following a similar procedure as described for the synthesis of **Example 14** from **Intermediate 26-1** instead of 1-[1-methyl-6-[6-(trideuteriomethylamino)-2-azaspiro[3.3]heptan-2-yl]indazol-3-yl] hexahydropyrimidine-2,4-dione (Step-5 product of intermediate 26-1 synthesis). LC/MS (ESI) *m/z* 856.4$[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21-9.99 (m, 2H), 8.82 (s, 1H), 7.93 (br d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 2.8 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.57 (br d, *J* = 2.9 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.92 (br d, *J* =

9.0 Hz, 2H), 6.79 (dd, *J* = 2.8, 8.4 Hz, 1H), 5.67 (tdd, *J* = 5.9, 10.6, 16.7 Hz, 1H), 5.05 (s, 1H), 5.03-4.96 (m, 1H), 4.86 (br d, *J* = 16.6 Hz, 1H), 4.81-4.70 (m, 1H), 4.63-4.52 (m, 1H), 4.47 (s, 2H), 3.87 (s, 2H), 3.76 (s, 2H), 3.63 (br d, *J* = 11.9 Hz, 2H), 3.36 (br s, 2H), 3.02-2.92 (m, 1H), 2.84-2.73 (m, 1H), 2.65-2.58 (m, 2H), 2.54 (br s, 2H), 2.49-2.45 (m, 1H), 2.33-2.26 (m, 2H), 2.21 (ddd, *J* = 5.6, 8.2, 13.4 Hz, 1H), 2.07-1.99 (m, 3H), 1.94 (br t, *J* = 8.2 Hz, 2H), 1.91-1.85 (m, 1H), 1.79 (br d, *J* = 11.0 Hz, 2H), 1.71 (dd, *J* = 7.3, 13.6 Hz, 1H), 1.64-1.51 (m, 1H), 1.25-1.16 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

Example 18

3-(5-(6-(((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)methyl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)piperidine-2,6-dione (**27**)





[0181] Step 1: To a solution of (2,6-dibenzyloxy-3-pyridyl)boronic acid (5 g, 14.92 mmol) and 2,5-dibromopyridine (5.30 g, 22.38 mmol) in dioxane (100 mL) was added Cs_2CO_3 (9.72 g, 29.84 mmol) and $Pd(dppf)Cl_2$ (1.09 g, 1.49 mmol). The mixture was stirred at 90 °C for 1 h. LCMS showed the starting material was consumed completely. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel (eluted with PE: EtOAc = 100: 0 to 10: 1) to give 2,6-dibenzyloxy-3-(5-bromo-2-pyridyl)pyridine (2.2 g, 29%). MS (ESI): *m/z* = 449.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.74 (d, *J* = 1.9 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.10-8.02 (m, 1H), 8.02-7.95 (m, 1H), 7.48-7.41 (m, 4H), 7.41-7.29 (m, 6H), 6.61 (d, *J* = 8.4 Hz, 1H), 5.50 (s, 2H), 5.40 (s, 2H).

[0182] Step 2: To a solution of 2,6-dibenzyloxy-3-(5-bromo-2-pyridyl)pyridine (1 g, 1.97 mmol) and *tert*-butyl *N*-(2-azaspiro[3.3]heptan-6-yl)-N-(trideuteriomethyl)carbamate (451.16 mg, 1.97 mmol) in dioxane (20 mL) was added Cs_2CO_3 (1.28 g, 3.93 mmol) and XPhos Pd G3 (166.52 mg, 196.73 μmol) under N_2. The mixture was stirred at 90 °C for 12 h. LCMS showed starting material was consumed completely and one main peak with desired

mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel (eluted with PE: EtOAc = 100: 0 to 0: 100) to give *tert*-butyl *N*-[2-[6-(2,6-dibenzyloxy-3-pyridyl)-3-pyridyl]-2-azaspiro[3.3]heptan-6-yl]-*N*-(trideuteriomethyl)carbamate (0.7 g, 49%). MS (ESI): *m/z* = 596.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.20 (d, *J* = 8.3 Hz, 1H), 7.95-7.76 (m, 2H), 7.55-7.24 (m, 10H), 6.81 (br dd, *J* = 2.6, 8.6 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 5.55-5.28 (m, 4H), 4.02-3.91 (m, 3H), 3.82 (s, 2H), 2.34 (br d, *J* = 8.3 Hz, 4H), 1.39 (s, 9H).

[0183] Step 3: To a suspension of Pd/C (232.22 mg, 218.21 μmol, 10% purity) in TFE (18 mL) was added *tert*-butyl *N*-[2-[6-(2,6-dibenzyloxy-3-pyridyl)-3-pyridyl]-2-azaspiro[3.3]heptan-6-yl]-*N*-(trideuteriomethyl)carbamate (0.65 g, 1.09 mmol) under Ar. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 24 h. LCMS showed the starting material was consumed completely. The suspension was filtered through a pad of celite and the filter cake was washed with TFE (50 mL). The filtrate was concentrated to give *tert*-butyl *N*-[2-[6-(2,6-dioxo-3-piperidyl)-3-pyridyl]-2-azaspiro[3.3]heptan-6-yl]-*N*-(trideuteriomethyl)carbamate (0.5 g, 63%), which was used for next step directly without further purification. MS (ESI): *m/z* = 418.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 10.81 (s, 1H), 7.77 (d, *J* = 2.5 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.92-6.67 (m, 1H), 4.32 (t, *J* = 7.1 Hz, 1H), 4.06-3.99 (m, 1H), 3.96 (s, 2H), 3.94-3.87 (m, 2H), 3.84 (s, 2H), 2.64 (br d, *J* = 3.4 Hz, 1H), 2.50-2.46 (m, 1H), 2.39 (br d, *J* = 8.5 Hz, 4H), 1.45 (s, 9H).

[0184] Step 4: To a solution of *tert*-butyl *N*-[2-[6-(2,6-dioxo-3-piperidyl)-3-pyridyl]-2-azaspiro[3.3]heptan-6-yl]-*N*-(trideuteriomethyl)carbamate (0.5 g, 691.35 μmol) in DCM (10 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 12 h. LCMS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give 3-[5-[6-(trideuteriomethylamino)-2-azaspiro[3.3]heptan-2-yl]-2-pyridyl]piperidine-2,6-dione (0.5 g), which was used for next step directly without further purification. MS (ESI): *m/z* = 318.2 $[M+H]^+$.

[0185] Step 5: To a solution of 3-[5-[6-(trideuteriomethylamino)-2-azaspiro[3.3]heptan-2-yl]-2-pyridyl] piperidine-2,6-dione (0.5 g, 1.16 mmol, TFA salt) and

1-(4-nitrophenyl)piperidine-4-carbaldehyde (271.49 mg, 1.16 mmol) in THF (10 mL) was added DIEA (299.57 mg, 2.32 mmol), the mixture was stirred at 25 °C for 10 min. Then AcOH (76.55 mg, 1.27 mmol) and $NaBH(OAc)_3$ (491.26 mg, 2.32 mmol) was added. The mixture was stirred at 25 °C for 12 h. LCMS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by reverse phase HPLC to give 3-[5-[6-[[1-(4-nitrophenyl)-4-piperidyl]methyl-(trideuteriomethyl)amino]-2-azaspiro[3.3]heptan-2-yl]-2-pyridyl]piperidine-2,6-dione (0.14 g, 22%) . MS (ESI): *m/z* = 536.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 10.81 (s, 1H), 8.09 (d, *J* = 9.5 Hz, 2H), 7.75 (d, *J* = 2.8 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 9.5 Hz, 2H), 6.84 (dd, *J* = 2.8, 8.4 Hz, 1H), 4.10 (br d, *J* = 12.4 Hz, 2H), 3.91 (s, 3H), 3.81 (s, 2H), 3.05 (br t, *J* = 12.0 Hz, 2H), 2.76-2.59 (m, 2H), 2.42-2.07 (m, 5H), 2.06-1.90 (m, 4H), 1.85 (br d, *J* = 11.6 Hz, 3H), 1.21-1.08 (m, 2H).

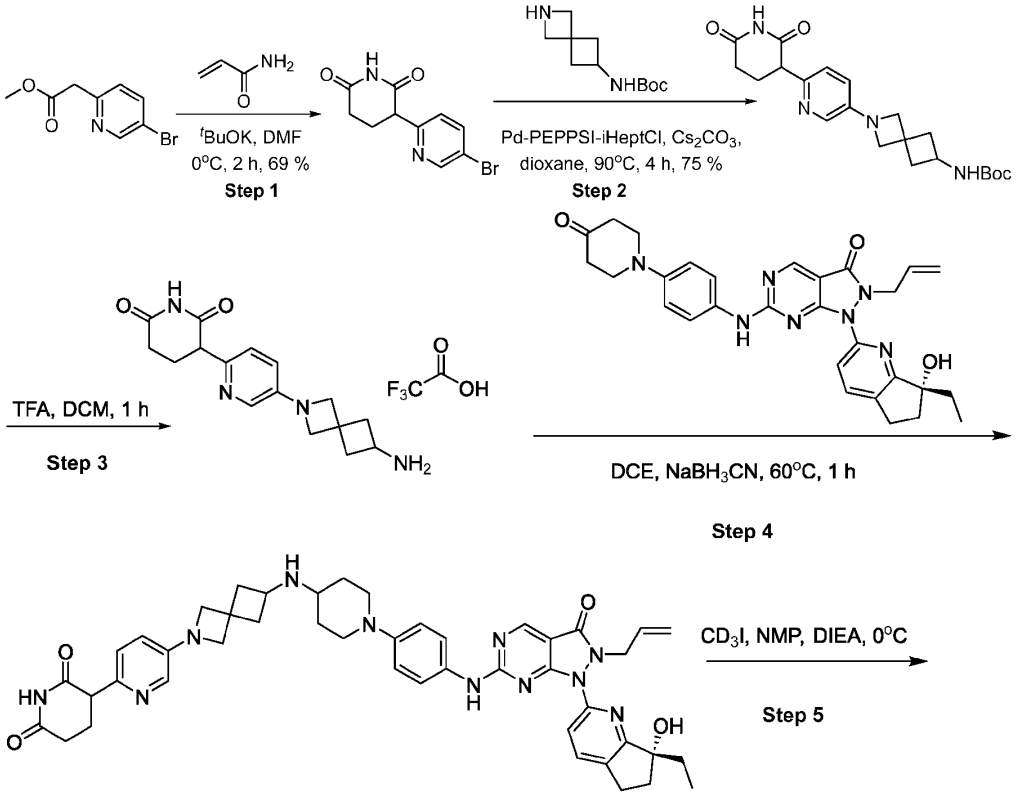
[0186] Step 6: To a flask purged with argon was charged with Pd/C (132.7 mg, 124.7 μmol, 10% purity) was added dioxane (2 mL). To the suspension was added a solution of 3-[5-[6-[[1-(4-nitrophenyl)-4-piperidyl]methyl-(trideuteriomethyl)amino]-2-azaspiro[3.3]heptan-2-yl]-2-pyridyl]piperidine-2,6-dione (0.14 g, 249.45 μmol) in dioxane (3 mL). The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 2 h. LCMS showed the starting material was consumed completely. The suspension was filtered through a pad of celite and the filter cake was washed with dioxane (10 mL). The filtrate was concentrated to give 3-[5-[6-[[1-(4-aminophenyl)-4-piperidyl]methyl-(trideuteriomethyl)amino]-2-azaspiro[3.3]heptan-2-yl]-2-pyridyl]piperidine-2,6-dione (0.12 g, 61%), which was used for next step directly without further purification. MS (ESI): *m/z* = 505.2 $[M+H]^+$.

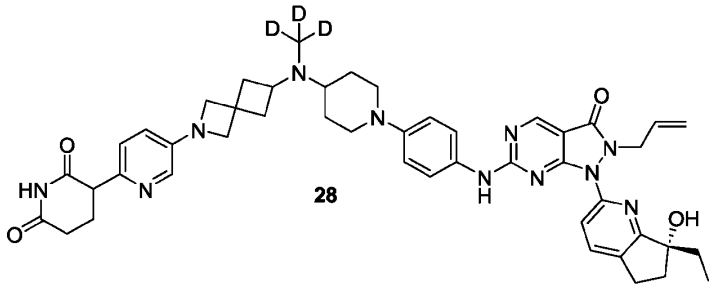
[0187] Step 7: To a solution of 3-[5-[6-[[1-(4-aminophenyl)-4-piperidyl]methyl-(trideuteriomethyl) amino]-2-azaspiro[3.3]heptan-2-yl]-2-pyridyl]piperidine-2,6-dione (0.12 g, 151.83 μmol,) in IPA (4 mL) was added 2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*] pyridin-2-yl]-6-methylsulfonyl-pyrazolo[3,4-d]pyrimidin-3-one (63.1 mg, 151.83 μmol). The mixture was stirred at 80 °C for 12 h. LCMS showed one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by reverse phaseHPLC to give 3-[5-[6-

[[1-[4-[[2-allyl-1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[*b*]pyridin-2-yl]-3-oxo-pyrazolo[3,4-d]pyrimidin-6-yl]amino]phenyl]-4-piperidyl]methyl-(trideuteriomethyl)amino]-2-azaspiro[3.3]heptan-2-yl]-2-pyridyl]piperidine-2,6-dione (51.3 mg, 39%) . MS (ESI): *m/z* = 841.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 10.75 (br s, 1H), 10.33-9.87 (m, 1H), 8.81 (br s, 1H), 7.92 (br s, 1H), 7.70 (br s, 2H), 7.56 (br s, 2H), 7.11 (br d, *J* = 7.8 Hz, 1H), 7.03-6.65 (m, 3H), 5.85-5.51 (m, 1H), 5.13-4.94 (m, 2H), 4.91-4.65 (m, 2H), 4.64-4.48 (m, 1H), 3.94-3.69 (m, 5H), 3.62 (br d, *J* = 9.8 Hz, 2H), 3.02-2.92 (m, 1H), 2.82-2.73 (m, 1H), 2.69-2.52 (m, 5H), 2.36-2.14 (m, 4H), 2.13-1.83 (m, 7H), 1.82-1.63 (m, 3H), 1.62-1.48 (m, 1H), 1.28-1.10 (m, 2H), 0.87 (br s, 3H).

Example 19

3-(5-(6-((1-(4-((2-Allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)piperidine-2,6-dione (**28**)





28

[0188] Step 1: To a solution of methyl 2-(5-bromopyridin-2-yl)acetate (2.9 g, 12.61 mmol) in DMF (10 mL) were added acrylamide (0.896 g, 12.61 mmol) and 1 M potassium *tert*-butoxide in THF (12.61 ml, 12.61 mmol) at 0 °C and the mixture was stirred at 0 °C for 2 h. LCMS showed a peak (55%) with desired mass. The mixture was poured into ice water (50 mL) and extracted with EtOAc (50 mL x 3), the combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography eluent of 0-20% EtOAc/ hexanes gradient to afford 3-(5-bromopyridin-2-yl)piperidine-2,6-dione (2.34 g, 8.70 mmol, 69%) . MS (ESI) *m/z*: 269 $[M+H]^-$.

[0189] Step 2: To a solution of *tert*-butyl (2-azaspiro[3.3]heptan-6-yl)carbamate (319 mg, 1.501 mmol) in 1,4-Dioxane (6 ml) was added 3-(5-bromopyridin-2-yl)piperidine-2,6-dione (404 mg, 1.501 mmol), cesium carbonate (978 mg, 3.00 mmol). The mixture was bubbled with nitrogen for 1 min before adding Pd-PEPPSI-iHeptCl (146 mg, 0.150 mmol). The reaction was heated at 90 °C for 4 h. The reaction was diluted with EtOAc (50 mL) and brine (50 mL). The organic layer was separated and aqueous was extracted with EtOAc (20 mL x 3). Combined organic layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by silica gel chromatography eluted with 0-100% EtOAc/Hexanes to give product *tert*-butyl (2-(6-(2,6-dioxopiperidin-3-yl)pyridin-3-yl)-2-azaspiro[3.3]heptan-6-yl)carbamate (450 mg, 1.124 mmol, 75%). MS (ESI) *m/z*: 401.2 $[M+H]^+$.

[0190] Step 3: *Tert*-butyl (2-(6-(2,6-dioxopiperidin-3-yl)pyridin-3-yl)-2-azaspiro[3.3]heptan-6-yl)carbamate (111 mg, 0.277 mmol) in DCM (2 ml) was added trifluoroacetic acid (0.5 ml, 6.53 mmol). The reaction was stirred at rt for 3 h. The reaction mixture was concentrated, and the residue was treated with Et_2O and sonicated. The resulting material was collected by centrifuge and dried. The 3-(5-(6-amino-2-azaspiro[3.3]heptan-2-

yl)pyridin-2-yl)piperidine-2,6-dione 2,2,2-trifluoroacetate was obtained as brown wax. MS (ESI) *m/z*: 301.2 $[M+H]^+$.

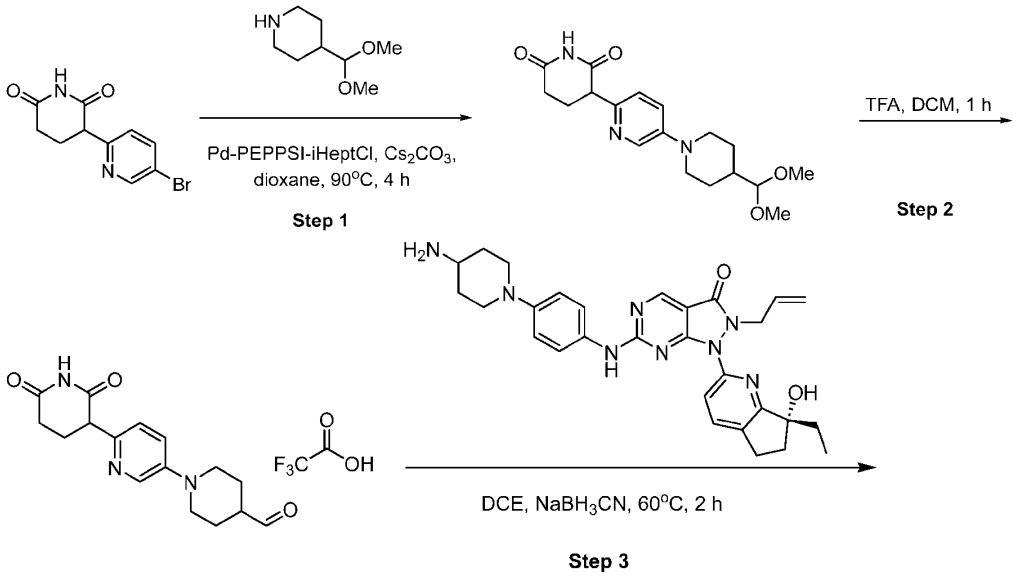
[0191] Step 4: To a stirred solution of 3-(5-(6-amino-2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)piperidine-2,6-dione 2,2,2-trifluoroacetate (115 mg, 0.278 mmol) in DCE (5 mL) was added *N*,*N*-diisopropylethylamine (2 mL, 11.48 mmol), then (*R*)-2-allyl-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[b]pyridin-2-yl)-6-((4-(4-oxopiperidin-1-yl)phenyl)amino)-1,2-dihydro-3*H*-pyrazolo[3,4-d]pyrimidin-3-one (100 mg, 0.190 mmol) . The reaction mixture was stirred at 60 °C for 1h. Reaction mixture was cooled to rt, sodium cyanoborohydride (47.8 mg, 0.761 mmol) was added and stirred at 60 °C for 1 h. The reaction mixture was loaded to column with celite. The product was purified by silica chromatography eluted with 0-10% DCM/MeOH. The product was further purified by reverse C18 column eluted with 0-100% MeCN/H_2O (with 0.1% formic acid). The pure product fractions were combined and concentrated. The residue was added saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered, concentrated to afford 3-(5-(6-((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)amino)-2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)piperidine-2,6-dione (50 mg, 32 %). was afforded. MS (ESI) *m/z*: 810.4 $[M+H]^+$.

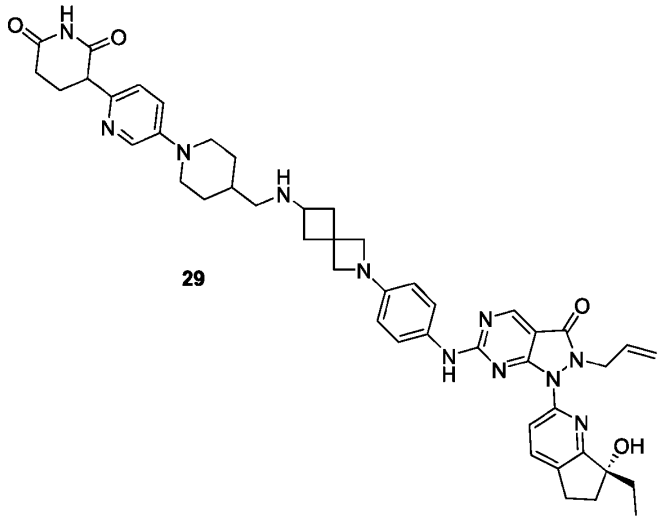
[0192] Step 5: The solution of 3-(5-(6-((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)piperidin-4-yl)amino)-2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)piperidine-2,6-dione (50 mg, 0.062 mmol) in NMP (3 mLl) was cooled in ice water and added DIEA (0.2 ml, 1.148 mmol). The solution of iodomethane-d_3 (13.42 mg, 0.093 mmol) in NMP (1 mL) was added above solution. The reaction was stirred at 0 °C for 3 h. The starting material was consumed. Reaction was diluted with EtOAc (50 mL) and ice water (50 mL). The organic layer was separated and aqueous was extracted with EtOAc (20 mL x 3). The product was purified by silica gel chromatography eluted with 0-10% MeOH in DCM. The pure product fractions were combined and concentrated. The product was dissolved in MeCN (1 mL) and water (1 mL). The solution of the product was frozen and lyophilized for 2 days to afford 3-(5-(6-((1-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-

yl)amino)phenyl)piperidin-4-yl)(methyl-d_3)amino)-2-azaspiro[3.3]heptan-2-yl)pyridin-2-yl)piperidine-2,6-dione (20 mg, 0.024 mmol, 39 %). was MS (ESI): m/z = 828.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 10.72 (s, 1H), 10.08 (s, 1H), 8.75 (s, 1H), 7.96-7.76 (m, 1H), 7.71-7.58 (m, 2H), 7.58-7.39 (m, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.86 (s, 2H), 6.77-6.67 (m, 1H), 5.70-5.40 (m, 1H), 5.01-4.96 (m, 1H), 4.95-4.88 (m, 1H), 4.83-4.75 (m, 1H), 4.74-4.61 (m, 1H), 4.57-4.41 (m, 1H), 3.85-3.81 (m, 2H), 3.81-3.74 (m, 1H), 3.71-3.67 (m, 2H), 3.67-3.56 (m, 2H), 3.07-2.96 (m, 1H), 2.96-2.84 (m, 1H), 2.77-2.65 (m, 1H), 2.63-2.49 (m, 2H), 2.28-2.19 (m, 2H), 2.18-2.05 (m, 2H), 2.03-1.90 (m, 4H), 1.88-1.76 (m, 1H), 1.68-1.61 (m, 1H), 1.60-1.53 (m, 2H), 1.53-1.43 (m, 2H), 1.25-1.06 (m, 3H), 0.84-0.77 (m, 3H).

Example 20

3-(5-(4-(((2-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)amino)methyl)piperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione (**29**)





29

[0193] Step 1: To a solution of 4-(dimethoxymethyl)piperidine (251 mg, 1.576 mmol) in 1,4-dioxane (6 mL) was added 3-(5-bromopyridin-2-yl)piperidine-2,6-dione (212 mg, 0.788 mmol) and cesium carbonate (513 mg, 1.576 mmol). The mixture was bubbled with nitrogen for 1 min before adding Pd-PEPPSI-iHeptCl (92 mg, 0.095 mmol). The reaction was heated at 90 °C for 4 h. the reaction was diluted with EtOAc (50 mL) and brine (50 mL). Organic layer was separated and aqueous layer was extracted with EtOAc (20 mL x 3). Combined organic layers were dried over Na_2SO_4. After filtration and concentration, the residue was purified by silica gel chromatography eluted with 0-100% EtOAc/hexanes to give product 3-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione (249 mg, 91 %) . MS (ESI): *m/z* = 348.2 $[M+H]^+$.

[0194] Step 2: The 3-(5-(4-(dimethoxymethyl)piperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione (249 mg, 0.717 mmol)in DCM (1 mL) was added trifluoroacetic acid (1 mL, 13.07 mmol). the reaction was stirred at rt for 0.5 h. The reaction mixture was concentrated, and the residue was treated with Et_2O and sonicated. The mixture was centrifuged, and solvent was decanted, then dried to afford 1-(6-(2,6-dioxopiperidin-3-yl)pyridin-3-yl)piperidine-4-carbaldehyde 2,2,2-trifluoroacetate (249 mg, 84%). MS (ESI): *m/z* = 302.1 $[M+H]^+$.

[0195] Step 3: To a stirred solution of 1-(6-(2,6-dioxopiperidin-3-yl)pyridin-3-yl)piperidine-4-carbaldehyde 2,2,2-trifluoroacetate (85 mg, 0.205 mmol) in DCE (5 mL) was added *N*,*N*-Diisopropylethylamine (0.5 mL, 2.87 mmol), then (*R*)-2-allyl-6-((4-(6-amino-2-

azaspiro[3.3]heptan-2-yl)phenyl)amino)-1-(7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-1,2-dihydro-3*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (92 mg, 0.171 mmol). The reaction mixture was stirred at 60 °C for 1h. Reaction mixture was cooled to rt, sodium cyanoborohydride (42.9 mg, 0.683 mmol) was added and stirred at 60 °C for 1 h. The reaction mixture was loaded to column with celite. The product was purified by silica chromatography eluted with 0-10% DCM/MeOH. The product was further purified by reverse C18 column eluted with 0-100% MeCN/H_2O (with 0.1% formic acid). The pure product fractions were combined and concentrated. To the residue was added saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and filtered, concentrated to afford 3-(5-(4-(((2-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)amino)methyl)piperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione (28.5 mg, 0.035 mmol, 20 %) . MS (ESI): *m/z* = 825.4 $[M+H]^+$.

[0196] Step 4: A solution of 3-(5-(4-(((2-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)amino)methyl)piperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione (28 mg, 0.034 mmol) in NMP (3 mL) was cooled in ice water and was added *N*-ethyl-*N*-isopropylpropan-2-amine (0.2 ml, 1.148 mmol). The solution of iodomethane-d_3 (6.40 mg, 0.044 mmol) in NMP (0.5 mL) was added to the above solution. The reaction was stirred at 0 °C for 3 h. The starting material consumed. The reaction was diluted with EtOAc (50 mL) and brine (50 mL). The organic layer was separated and aqueous was extracted with EtOAc (20 mL x 3). The product was purified by silica gel chromatography eluted with 0-10% MeOH in DCM. The pure product fractions were combined and concentrated. The product was dissolved in MeCN (1 mL) and water (1 mL). The solution of the product was frozen and lyophilized for 2 days to afford 3-(5-(4-(((2-(4-((2-allyl-1-((*R*)-7-ethyl-7-hydroxy-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)-3-oxo-2,3-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)amino)phenyl)-2-azaspiro[3.3]heptan-6-yl)(methyl-d_3)amino)methyl)piperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione (16.7 mg, 55 %). MS (ESI): *m/z* = 842.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 10.72 (s, 1H), 9.95 (s, 1H), 8.72 (s, 1H), 8.18-8.08 (m, 1H), 7.86-7.76 (m, 1H), 7.66-7.55 (m, 1H), 7.53-7.32 (m, 2H),

7.27-7.14 (m, 1H), 7.12-7.03 (m, 1H), 6.38-6.26 (m, 2H), 5.92 (d, J = 7.0 Hz, 1H), 5.65-5.50 (m, 1H), 4.98 (s, 1H), 4.95-4.92 (m, 1H), 4.92-4.87 (m, 1H), 4.83-4.74 (m, 1H), 4.73-4.63 (m, 1H), 4.55-4.42 (m, 1H), 3.84-3.76 (m, 1H), 3.75-3.68 (m, 2H), 3.68-3.58 (m, 4H), 2.97-2.80 (m, 1H), 2.75-2.65 (m, 1H), 2.29-2.19 (m, 3H), 2.17-2.06 (m, 4H), 2.05-1.98 (m, 1H), 1.99-1.90 (m, 3H), 1.90-1.78 (m, 3H), 1.76-1.67 (m, 2H), 1.66-1.56 (m, 2H), 1.18-1.04 (m, 2H), 0.83-0.76 (m, 3H).

Example 21
Cell proliferation_assay

[0197] Cell proliferation was measured using the CellTiter-Glo® Luminescent Cell Viability Assay. The assay involved the addition of a single reagent (CellTiter-Glo® Reagent) directly to cells cultured in serum-supplemented medium. A427 cells (ATCC, HTB-53), OVCAR3 (ATCC, HTB-161) and MDA-MB-231 (ATCC, CRM-HTB-26) cells were cultured according to ATCC recommendations and were seeded at 3,000 cells for A427, 5000 cells for OVCAR3 and 3000 for MDA-MB-231 cells per well.

[0198] Each compound evaluated was prepared as a DMSO stock solution (10 mM). Compounds were tested in duplicate on each plate, with a 10-point serial dilution curve (1:3 dilution). The highest compound concentration was 10 μM (final), with a 0.1% final DMSO concentration. Plates were then incubated at 37 °C, 5% CO_2 for 72 h for A427 or 6 day for OVCAR3 and MDA-MB-231, and then were equilibrated at rt for approximately 30 mins. An equi-volume amount of CellTiter-Glo® Reagent (100 μL) was added to each well. Plates were mixed for 2 mins on an orbital shaker to induce cell lysis and then incubated at rt for 10 mins to stabilize the luminescent signal. Luminescence was recorded using a Spectramax i3x (Molecular Devices) plate reader according to CellTiter-Glo protocol. IC_{50} determination was performed using a non-linear regression, variable slope (four parameter), inhibitor v. response equation (Prism 9.0). IC_{50} values are provided in Table 2. For comparison, Table 2 also includes IC_{50} values for reference compound ZN-c3.

Table 2. IC_{50} values.

Compound No.	A427 (nM)	OVCAR3 (nM)	MDA-MB-231 (nM)
1	A	A	A

Compound No.	A427 (nM)	OVCAR3 (nM)	MDA-MB-231 (nM)
2	ND	ND	B
3	A	A	A
4	A	B	A
5	A	A	A
6	A	A	A
7	A	A	A
8	A	A	A
9	A	A	A
10	A	A	A
11	A	A	A
12	A	B	A
13	A	A	A
14	A	A	A
15	A	A	A
16	A	A	A
17	A	B	B
26	A	A	A
27	A	A	A
28	A	B	B
29	A	A	A
30	A	A	A
31	A	B	B
32	A	A	A
33	B	B	B
35	A	A	A
ZN-c3 (Reference)	B	B	B

For A427, OVCAR3 and MDA-MB-231 CTG IC_{50}: A = a single $IC_{50} \leq 100$ nM; B = a single $IC_{50} > 100$ nM and < 500 nM; C = a single $IC_{50} \geq 500$ nM, ND: Not Determined

Example 22
Protein degradation assay in MOLT-4 cells

[0199] 1.5 million MOLT-4 cells (ATCC, CRL-1582) were incubated with vehicle (DMSO) or 10 μM, 1 μM, 0.1 μM, or 0.01 μM concentrations of the indicated compounds for 5 hours. After treatment, the cells were harvested in RIPA lysis buffer supplemented with 1% Phosphatase Inhibitor and Protease Inhibitor Cocktail and protein concentration was determined by BCA assay. An equal amount of protein (3.5 μg/lane) from each cell extract was loaded onto 12-230 KDa Separation 25 Capillary Cartridges from

ProteinSimple and probed with WEE1 (1:200 dilution, final concentration of 1 μg/mL) and β-Actin (1:100 dilution, final concentration of 5 μg/mL) antibodies on a ProteinSimple Jess system according to ProteinSimple/SimpleWestern protocols. The area under the curve (AUC) from the resulting eletropherograms for each protein peak at the concentrations tested was used to calculate percent degradation for WEE1 using the equation percent degradation = 100 – [100*(WEE1/β-Actin)/($WEE1_{DMSO}$/$β\text{-Actin}_{DMSO}$)]. For illustrative purposes, electopherograms were exported as virtual blots using Compass for SW v 6.0 (ProteinSimple). The WEE-1 antibody (sc-5285) was purchased from Santa Cruz Biotechnology and β-actin (MAB8929) was purchased from R&D Systems. Percent remaining of WEE1 after 5 hour treatment in MOLT-4 cells at the tested concentrations are provided in Table 3. A "hook effect" is observed at higher concentrations, however these results indicate that many of the exemplified compounds are potent degraders of WEE1.

Table 3. Percent of remaining WEE1.

Percent remaining of WEE1 after 5 hours in MOLT-4 cells				
Compound No.	0.01 μM	0.1 μM	1 μM	10 μM
1	60	20	13	22
2	83	41	14	15
3	60	17	11	21
4	59	18	12	28
5	57	16	12	30
6	58	16	14	30
7	63	19	12	24
8	60	15	15	35
9	70	19	16	35
10	52	15	11	27
11	55	19	11	24
12	61	19	13	31
13	72	17	10	11
15	9	7	10	ND
16	12	17	46	ND
17	31	10	20	ND
26	10	12	37	ND

Percent remaining of WEE1 after 5 hours in MOLT-4 cells				
Compound No.	0.01 μM	0.1 μM	1 μM	10 μM
27	11	7	15	ND
28	42	75	105	ND
29	11	12	58	ND
30	14	8	21	ND
31	31	10	20	ND
32	6	5	14	ND
33	21	15	36	ND
35	ND	ND	ND	ND

[0200] Compounds of Formula (I) or Formula (I') provided herein exhibit highly desirable properties for a DNA damage response (DDR) kinase inhibitor/degrader, including cancer cell proliferation and WEE1 kinase degradation as demonstrated in the data presented in Tables 2 and 3. In addition, compounds of Formula (I) or Formula (I') exhibit superior solubility as well as *in vivo* safety and pharmacokinetic-pharmacodynamic properties as characterized using assay methods readily known by a person having ordinary skill in the art, such as the methods described in the following Examples 23-26.

Example 23

Metabolic stability of WEE1 inhibitor/degrader compounds in mouse, rat, dog, monkey, and human microsomes

[0201] 222.5 μL of the master solution (100 mM phosphate buffer; 1 mg/mL liver microsomes) and 25 μL of 20 mM NADPH solution were added to the incubation plates and pre-warmed for 10 min. Each reaction was started with the addition of 2.5 μL of 100 μM control compound or test compound solutions. Verapamil was used as positive control in this study. The final concentration of control compound and test compounds were 1 μM. Aliquots of 25 μL were taken from the reaction solution at 0.5, 15, 30, 60 and 120 min. Each reaction was stopped by the addition of 5 volumes of cold acetonitrile with IS (100 nM Alprazolam, 200 nM Caffeine, 200 nM Labetalol and 100 nM tolbutamide). Samples were centrifuged at 3, 220 g for 30 min. Aliquots of 100 μL of the supernatant were mixed with 100 μL of ultra-pure H_2O and then used for LC-MS/MS analysis.

[0202] All calculations were carried out using Microsoft Excel. Peak area ratios were determined from extracted ion chromatograms. Percent compounds remaining at each time point were calculated by the following equation:

Remaining Percentage t min (%) = [Peak Area Ratio t min/Peak Area Ratio 0 min] × 100%

Where:

Peak Area Ratio t min is peak area ratio of control and test compounds at t min;

Peak Area Ratio 0 min is peak area ratio of control and test compounds at zero time point.

[0203] Peak areas were determined from extracted ion chromatograms. The slope value, *k*, was determined by linear regression of the natural logarithm of the remaining percentage of the parent drug vs. incubation time curve.

[0204] The *in vitro* half-life (*in vitro*$_{t1/2}$) was determined from the slope value:

[0205] *in vitro* $t_{1/2} = -(0.693 / k)$

[0206] Conversion of the *in vitro*$_{t1/2}$ (min) into the *in vitro* intrinsic clearance (*in vitro* CL_{int}, in µL/min/mg protein) was done using the following equation (mean of duplicate determinations):

$$\textit{in vitro}\ CL_{int} = \left(\frac{0.693}{(t_{1/2})}\right) * \left(\frac{\text{volume of incubation (µL)}}{\text{amount of proteins (mg)}}\right)$$

[0207] The calculations of Cl_{int} (mL/min/kg), Pred Cl (mL/min/kg) and ER (endoplasmic reticulum) were done using the following equations:

$Cl_{int} = (0.693/T_{1/2}) \times (1/(\text{microsomal protein concentration (0.5 mg/mL)})) \times \text{Scaling Factors}$ (*see* Table for scaling factors)

$Cl_{hep} = (QH \times Cl_{int} \times fub) / (QH + Cl_{int} \times fub)$

$ER = Cl_{hep}/QH$, where QH is the hepatic blood flow (mL/min/kg) (Table 4), fub is the fraction of unbound drug in plasma which is assumed to be 1.

Table 4. Scaling factors for intrinsic clearance prediction in mouse, rat, dog, monkey, and human microsomes.

Species	Microsomal Protein per Gram of Liver	Liver Weight per Kilogram of Body Weight	Scaling Factor[a]	Hepatic Blood Flow (mL/min/kg)
Human	40	25.7	1028	21

Species	Microsomal Protein per Gram of Liver	Liver Weight per Kilogram of Body Weight	Scaling Factor[a]	Hepatic Blood Flow (mL/min/kg)
Monkey	40	30	1200	44
Dog	55	32	1760	31
Rat	46	40	1840	78
Mouse	47	88	4136	126

[a] Scaling Factor = (microsomal protein per gram of liver) × (liver weight per kilogram of body weight)

Example 24

LogD determination of WEE1 inhibitors/degraders in 1-octanol/PBS pH 7.4

[0208] LogD is a distribution coefficient widely used to measure the lipophilicity of ionizable compounds, where the partition is a function of the pH.

[0209] The stock solutions of test compounds and the control compound were prepared in DMSO at the concentration of 10 mM. To prepare sodium phosphate buffer/octanol, equal amounts of freshly prepared 10 mM sodium phosphate buffer pH 7.4 and octanol were mixed and the two layers were vortexed thoroughly. The two layers were allowed to separate for several days in one glass separatory funnel. The first 5 mL of buffer from the separation funnel was discarded before filling the dispenser. The octanol-saturated of phosphate buffer was in the lower layer; the upper layer was octanol saturated with buffer.

[0210] 5 μL of stock solutions (10 mM) of each sample was placed in order into a 96-well plate. DMSO was added to make a total volume of 50 μL, with the final concentration of each test compound being 1 mM. 10 μL of 1 mM working solution of each compound was placed in order into their respective vials on the 96-well plate. 500 μL of saturated octanol was added into each vial of the plate, followed by the addition of 500 μL of saturated phosphate buffer. The plate was then sealed and transferred to the Eppendorf Thermomixer Comfort plate shaker and shaken at 25°C, 2,000 rpm for 2 hours. The samples were centrifuged at 4,000 rpm at 25°C for 30 min to separate the phases. 5 μL of the octanol samples was transferred to a new 96-well plate, followed by addition of 495 μL of a mixture of H_2O and acetonitrile containing internal standard (1:1) as 100-fold octanol samples. The mixtures were vortexed for 5 min at 1,000 rpm. 50 μL of 100-fold samples were transferred

to new 96-well plate, followed by addition of 450 µL of a mixture of H_2O and acetonitrile containing internal standard (1:1) as 1,000-fold octanol samples. The samples were vortexed for 5 minutes at 1,000 rpm. 50 µL of the buffer samples were transferred to new 96-well plate, followed by addition of 450 µL of a mixture of H_2O and acetonitrile containing internal standard (1:1) as 10-fold buffer samples. The mixtures were vortexed for 5 min at 1,000 rpm.

[0211] The samples were evaluated by LC-MS/MS analysis. All calculations were carried out using Microsoft Excel. The LogD value of each compound was calculated as follows, with DF = dilution factor:

$$LogD = Log\left(\frac{AREA_{Oct} \times DF}{AREA_{Buf} \times DF}\right)$$

Example 25
CYP inhibition studies with midazolam

[0212] The CYP inhibition was determined by incubation of human liver microsome (HLM) with CYP substrates (for example, midazolam for CYP3A4 isoform) in presence of test compounds or control compounds. The incubations were carried out in 96-deep well plates. The following volumes were dispensed into each well of an incubation plate: 179 µL of the substrate solution (containing 1 µM substrate) and HLM mixture in phosphate buffer (100 mM, pH 7.4) and 1 µL of each test compound (at the concentrations 0, 20, 60, 200, 600, 2000 and 6000 µM in DMSO) and positive control working solution (ketoconazole at the concentrations 0, 0.0015, 0.005, 0.015, 0.05, 0.15 and 0.5 µM), or the vehicle. The incubation plate was placed into the water bath and pre-warmed at 37°C for 15 minutes before the reactions were started by the addition of 20 µL of 10 mM NADPH solution in phosphate buffer. After the addition of NADPH, the incubation plate was incubated at 37°C for 5 min. The assays were performed in duplicates.

[0213] At the end of the incubation, the reactions were quenched by the addition of 1 volume (200 µL) of cold acetonitrile containing 3% formic acid and internal standards (IS, 250 nM labetalol, 80 nM alprazolam and 300 nM tolbutamide). The plate was centrifuged at 4000 rpm for 30 min. The plate was then placed for 20 min on ice, then centrifuged at 4000 rpm for 30 min again to precipitate protein. 100 µL of the supernatant was transferred to a new plate. Samples were using UPLC/MS/MS. The automatic peak integration areas were

checked for all of the samples, including the Analyte Peak Area and Internal Standard Peak Area. The inhibition of each P450 enzyme in human liver microsomes was measured as the percentage decrease in the activity of marker metabolite formation compared to non-inhibited controls (= 100% activity):

$$Area\ Ratio = Peak\ Area_{Analyte} / Peak\ Area_{Internal\ Standard}$$

$$Remaining\ Activity\ (\%) = Area\ Ratio_{test\ compound} / Area\ Ratio_{vehicle} * 100\%$$

[0214] IC_{50} values (compound concentration which produces 50% inhibition) were determined using Excel XLfit 5.3.1.3.

Example 26

Pharmacokinetic studies of WEE1 inhibitors/ degraders in mice, rats, and dogs

[0215] Pharmacokinetic (PK) studies of test compounds and a control compound via oral gavage (PO) and intravenous (IV) administrations in male CD1 mice (6-8 weeks, ~20-30 g), male SD rats (6-8 weeks, ~200-300 g), and male beagle dogs (1-2.5 years, ~8-12 kg) were carried in accordance with the study designs described in Tables 5-7 below:

Table 5. PK mice study design for each test and control compound.

Group	Treatment	Dose Level (mg/kg)	Dose Volume (mL/kg)	Conc. (mg/mL)	Administration Route	No. of Animals
1	COMPOUND	3	5	0.6	IV	3MALE
2		10	10	1	PO	3MALE

Table 6. PK rat study design for each test and control compound.

Group	Treatment	Dose Level (mg/kg)	Dose Volume (mL/kg)	Conc. (mg/mL)	Administration Route	No. of Animals
1	COMPOUND	3	5	0.6	IV	3MALE
2		60	10	6	PO	3MALE

Table 7. PK dog study design for each test and control compound.

Group	Treatment	Dose Level (mg/kg)	Dose Volume (mL/kg)	Conc. (mg/mL)	Administration Route	No. of Animals
1	COMPOUND	3	2	1.5	IV	3MALE
2		10	5	2	PO	3MALE

[0216] With mice, all animals for IV and PO administration were not fasted prior to dosing. With rats, animals were food fasted overnight prior to dosing and were fed 4 hours after dosing. With dogs, the animals for PO administration were food fasted overnight prior to dosing and will be fed approximately 2 hours after dosing. The animals for IV groups had free access to food and water.

[0217] With all animals, the dose formulations were always freshly prepared on the day of dosing, with the vehicle composition being: DMSO/PEG400/30% HP-β-CD in water (5/20/75) for IV; 25% HP-β-CD in 25 mM citrate buffer (pH 3.0) for PO.

[0218] All animals were subject to the following PK schedule. The blood collection sites for the animals were the dorsal metatarsal vein (for mice), jugular vein (for rats), and peripheral veins (for dogs).

Table 8. PK schedule for mice, rats, and dogs.

Group	PK time points
IV	9 Time points: 5, 15, 30 min, 1, 2, 4, 8, 12 and 24 hrs post dose.
PO	8 Time points: 15, 30 min, 1, 2, 4, 8, 12 and 24 hrs post dose.

[0219] Verapamil and dexamethasone are normally used as internal standards. The standard curves were run in duplicates with a minimum of six standards, and a minimum of five standards and the LLOQ should fall within ±20% of the nominal value. The lower limit of quantitation (LLOQ) had a minimum signal to noise ratio of 3. A minimum of duplicate quality controls (QC's) at three concentrations (low, mid, and high QC) were incorporated into each run with the low QC no more than 3 x LLOQ, the mid QC around the middle of the curve, and the high QC were 80% of the ULOQ for the run. The results of the QC's provided the basis for accepting or rejecting the run. At least 67% of all QC's, or four

of six should be within 20% of their respective nominal values; 33% of the QC's fell outside 20% of nominal value. At least 50% of the of the QC's at the same concentration were within 20% of their respective nominal values. The simplest model that adequately describes the concentration-response relationship was used. Linear or quadratic regressions were also used.

[0220] Concentrations of each test or control compound in the plasma samples were analyzed using an LC-MS/MS method.

[0221] WinNonlin (Phoenix^{TM}, version 8.3) or other similar software will be used for pharmacokinetic calculations. The following pharmacokinetic parameters will be calculated, whenever possible, from the plasma concentration versus time data:

IV administration: $T_{1/2}$, C_0, AUC_{last}, AUC_{0-24h}, AUC_{inf}, MRT_{inf}, Cl, Vss, Number of Points for Regression.

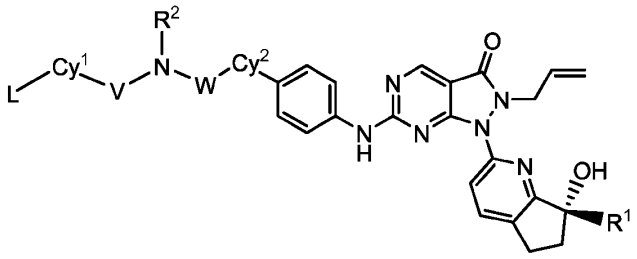
PO administration: $T_{1/2}$, C_{max}, T_{max}, AUC_{last}, AUC_{0-24h}, AUC_{inf}, Bioavailability (F).

[0222] The pharmacokinetic data was described using descriptive statistics such as mean, standard deviation.

[0223] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the disclosure.

WHAT IS CLAIMED IS:

1. A compound of Formula (I'), or a pharmaceutically acceptable salt thereof, having the structure:



(I')

wherein:

Cy^1 and **Cy^2** are each independently a substituted or an unsubstituted 4- to 11-membered heterocyclyl;

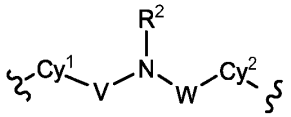
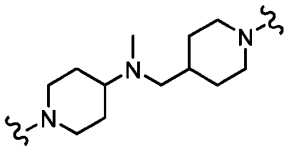
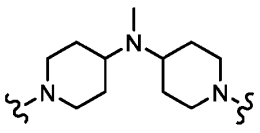
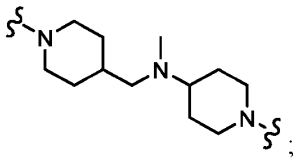
V and **W** are each independently absent or $-CH_2-$;

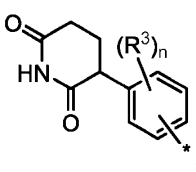
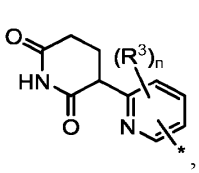
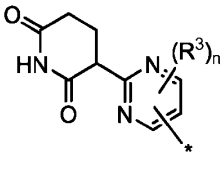
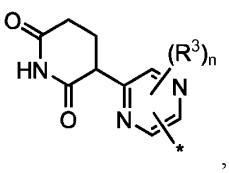
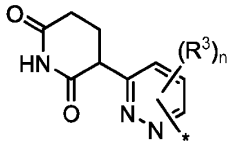
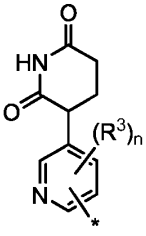
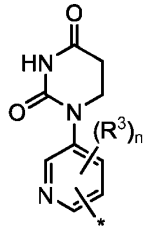
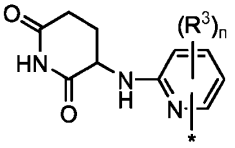
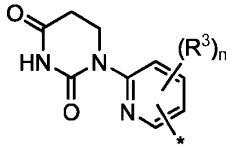
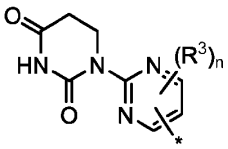
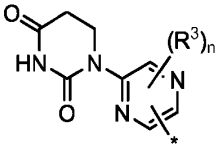
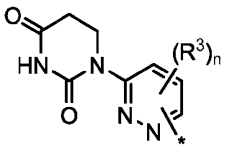
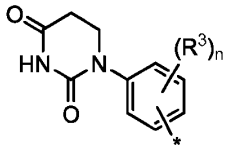
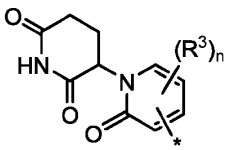
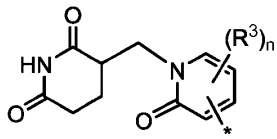
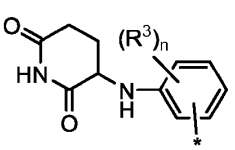
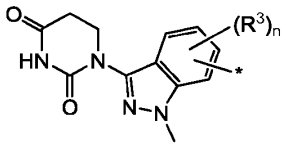
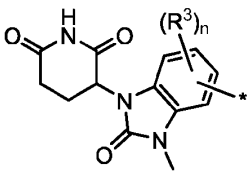
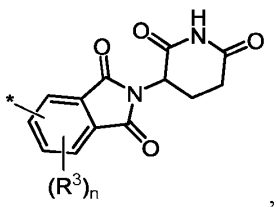
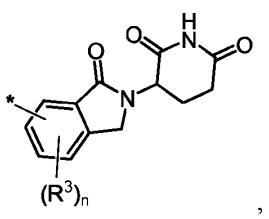
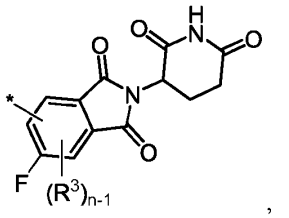
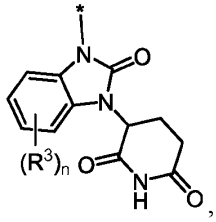
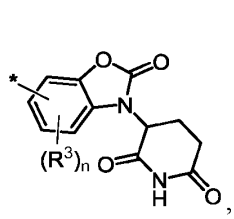
R^1 is a substituted or an unsubstituted C_1-C_6 alkyl;

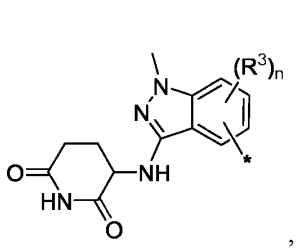
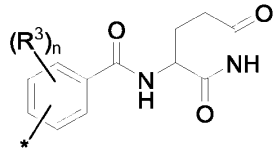
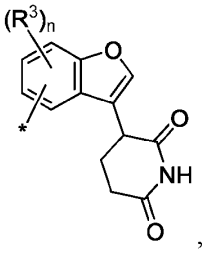
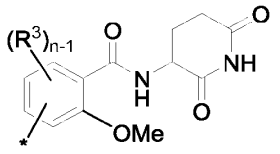
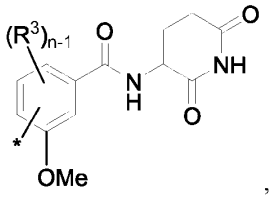
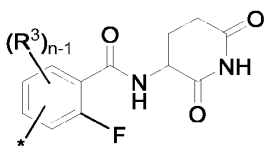
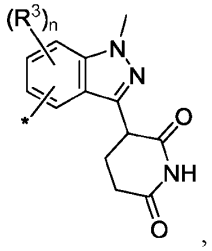
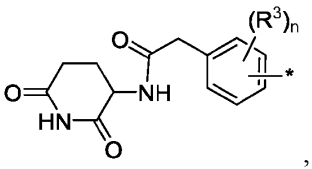
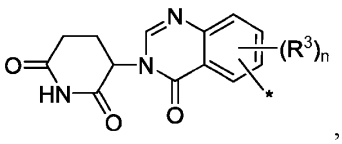
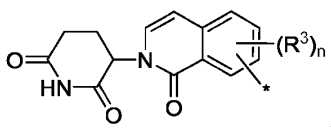
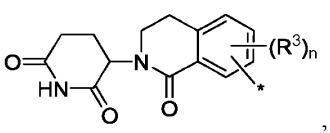
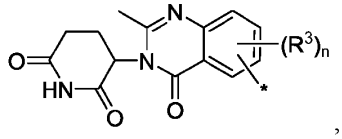
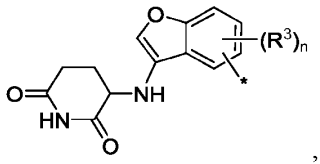
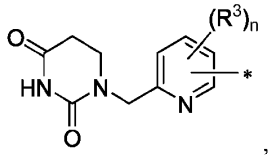
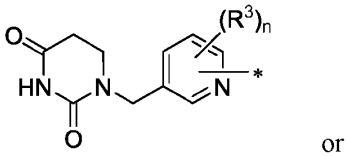
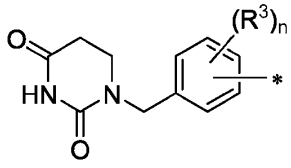
R^2 is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-C_xH_yD_z$; wherein:

x is an integer selected from 1, 2, 3 and 4;

y is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7 and 8; and

z is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8 and 9; provided that the sum of **y** and **z** is 2**x** + 1 and with the proviso that  is not ,  or ;

L is , , , , , , , , , , , , , , , , , , , , , , .

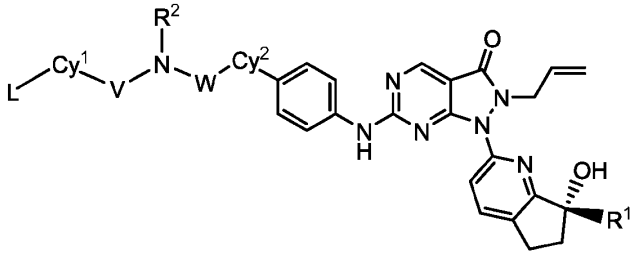

,

,

,

,

,

,

,

,

,

,

,

,

,

,

or

; wherein:

* indicates the point of attachment to **Cy[1]**;

R[3] is halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl or C_1-C_4 alkoxy; and

n is 0, 1 or 2.

2. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, having the structure:



(I)

wherein:

Cy¹ and **Cy²** are each independently a substituted or an unsubstituted 4- to 11-membered heterocyclyl;

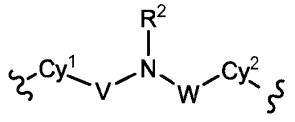
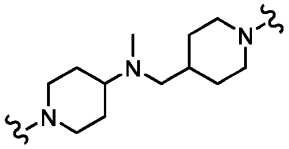
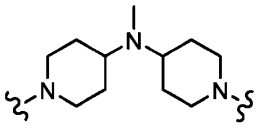
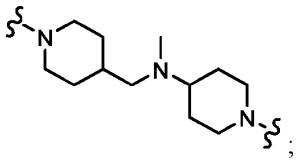
V and **W** are each independently absent or $-CH_2-$;

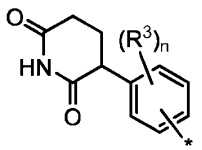
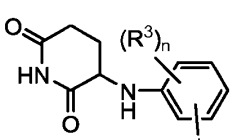
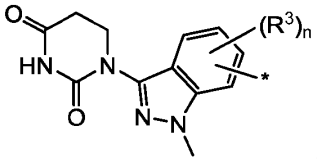
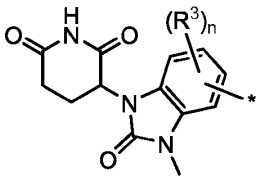
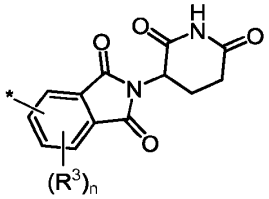
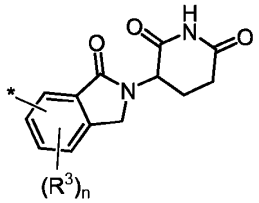
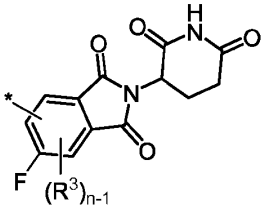
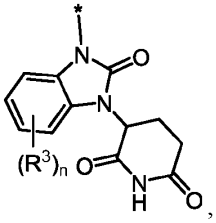
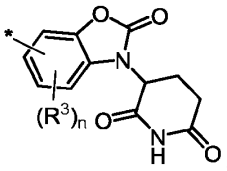
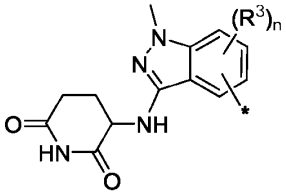
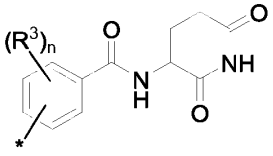
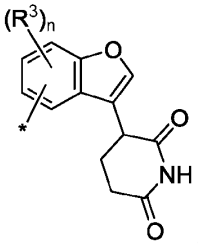
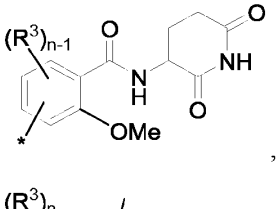
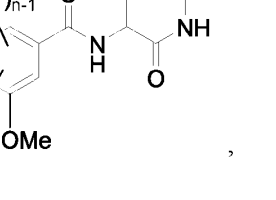
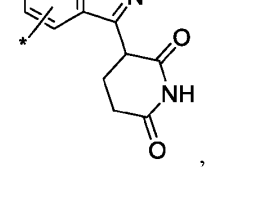
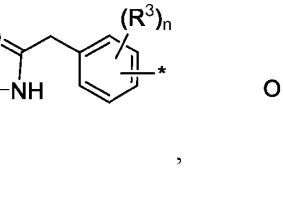
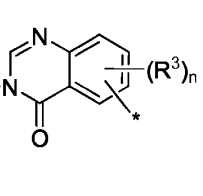
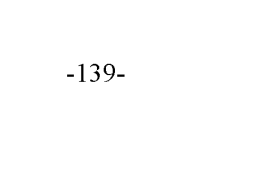
R¹ is a substituted or an unsubstituted C_1-C_6 alkyl;

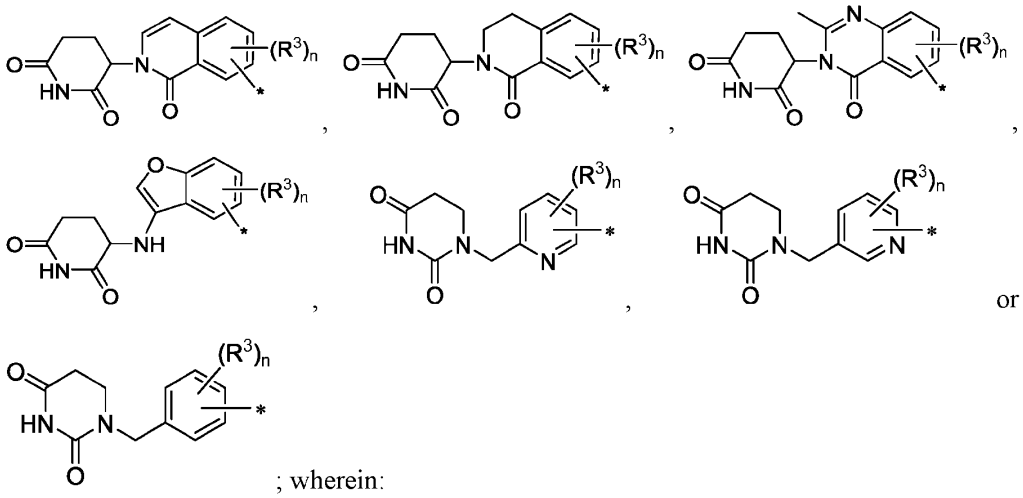
R² is C_1-C_4 alkyl, C_1-C_4 haloalkyl or $-C_xH_yD_z$; wherein:

x is an integer selected from 1, 2, 3 and 4;

y is an integer selected from 0, 1, 2, 3, 4, 5, 6, 7 and 8; and

z is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8 and 9; provided that the sum of **y** and **z** is 2**x** + 1 and with the proviso that  is not ,  or ;

L is , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , .



; wherein:

* indicates the point of attachment to **Cy^1**;

R^3 is halogen, C$_1$-C$_4$ alkyl, C$_1$-C$_4$ haloalkyl or C$_1$-C$_4$ alkoxy; and

n is 0, 1 or 2.

3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein **V** and **W** are both absent.

4. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein **V** is absent and **W** is $-CH_2-$.

5. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein **V** is $-CH_2-$ and **W** is absent.

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein **Cy^1** and **Cy^2** are each independently an unsubstituted 4- to 11-membered heterocyclyl or a 4- to 11-membered heterocyclyl substituted with one or more groups selected from halogen, C$_1$-C$_4$ alkyl, C$_1$-C$_4$ haloalkyl and C$_1$-C$_4$ alkoxy.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein **Cy^1** and **Cy^2** are each independently an unsubstituted 4- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms and optionally 1 or 2 oxygen atoms or a 4- to 11-membered heterocyclyl containing 1 or 2 nitrogen atoms and optionally 1 or 2 oxygen atoms substituted with one or more groups selected from halogen, C$_1$-C$_4$ alkyl, C$_1$-C$_4$ haloalkyl and C$_1$-C$_4$ alkoxy.

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein **Cy^1** and **Cy^2** are each independently azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 2-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 2-azaspiro[3.4]octanyl, 2,6-diazaspiro[3.4]octanyl, 1-oxa-7-azaspiro[4.4]nonanyl, 5-oxa-2-azaspiro[3.4]octanyl or 1-oxa-9-azaspiro[5.5]undecanyl, each optionally substituted with one or more groups selected from F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl and C_1-C_4 alkoxy.

9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein **Cy^1** and **Cy^2** are each independently azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, 2-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 2-azaspiro[3.4]octanyl or 2,6-diazaspiro[3.4]octanyl, each optionally substituted with one or more groups selected from F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl and C_1-C_4 alkoxy.

10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein **Cy^1** is piperidinyl and **Cy^2** is 2-azaspiro[3.3]heptanyl.

11. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein **Cy^1** and **Cy^2** are each piperidinyl.

12. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein **Cy^1** is 2-azaspiro[3.3]heptanyl and **Cy^2** is piperidinyl.

13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **R^2** is C_1-C_4 alkyl or $-C_xH_yD_z$..

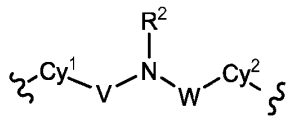
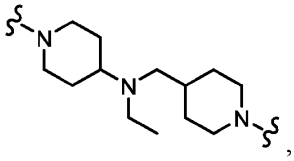
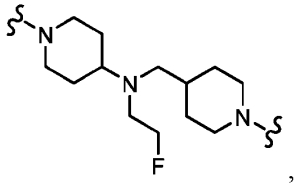
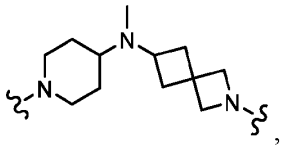
14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein **R^2** is $-C_xH_yD_z$..

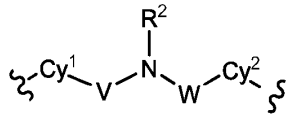
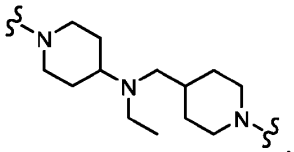
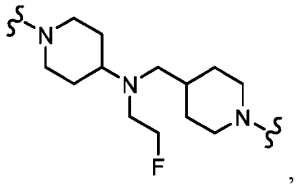
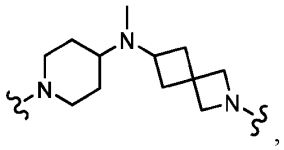
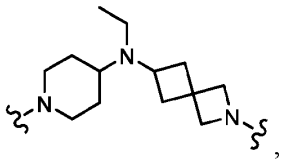
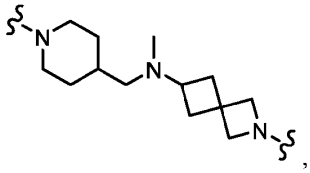
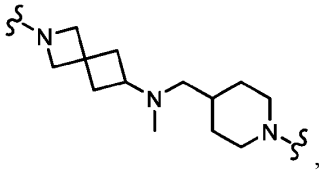
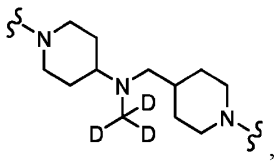
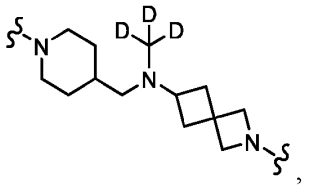
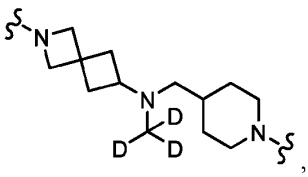
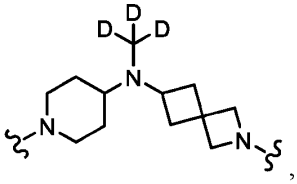
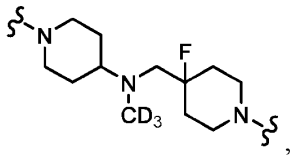
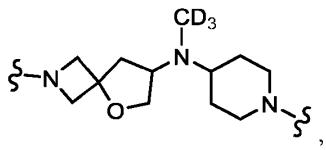
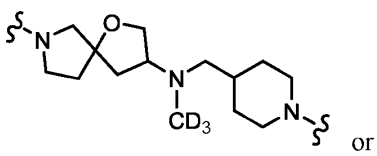
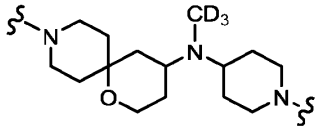
15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein **R^2** is $-CD_3$, $-CHD_2$, $-CDH_2$, $-C_2D_5$, $-C_2HD_4$, $-C_2H_2D_3$, $-C_2H_3D_2$ or $-C_2DH_4$.

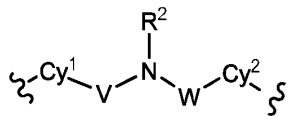
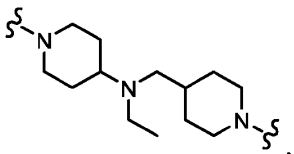
16. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein **R^2** is C_1-C_2 alkyl, C_1-C_2 fluoroalkyl, $-CD_3$, $-CHD_2$, $-CDH_2$, $-C_2D_5$, $-C_2HD_4$, $-C_2H_2D_3$, $-C_2H_3D_2$ or $-C_2DH_4$.

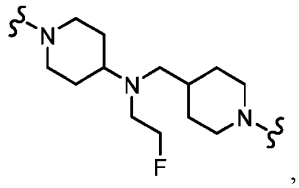
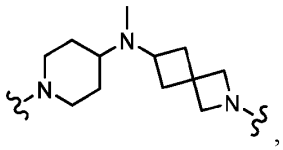
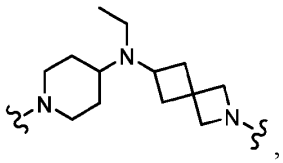
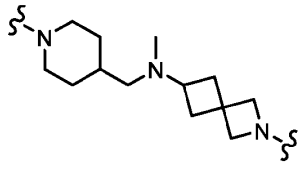
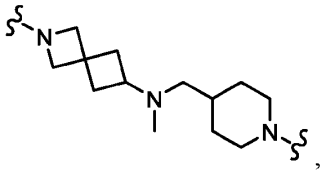
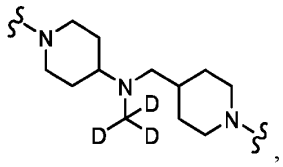
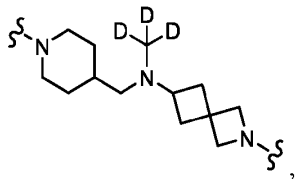
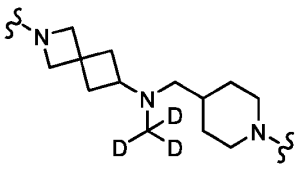
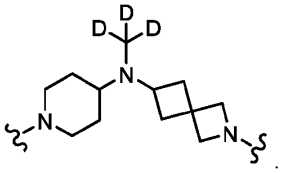
17. The compound of claim 16, or a pharmaceutically acceptable salt thereof, wherein **R^2** is $-CH_3$, $-C_2H_5$, $-C_2H_4F$ or $-CD_3$.

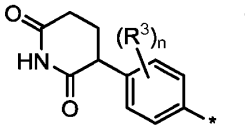
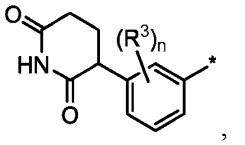
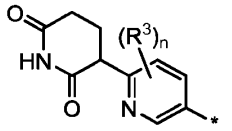
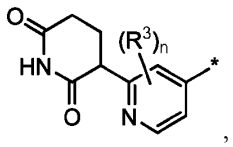
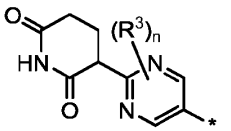
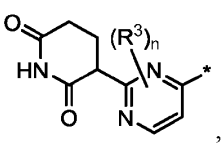
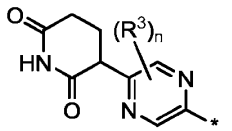
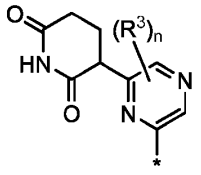
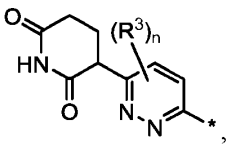
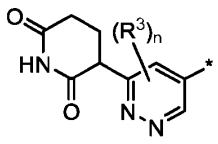
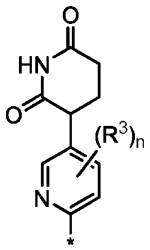
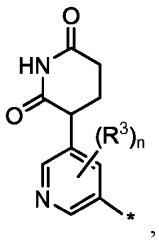
18. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^2}$ is $-CD_3$.

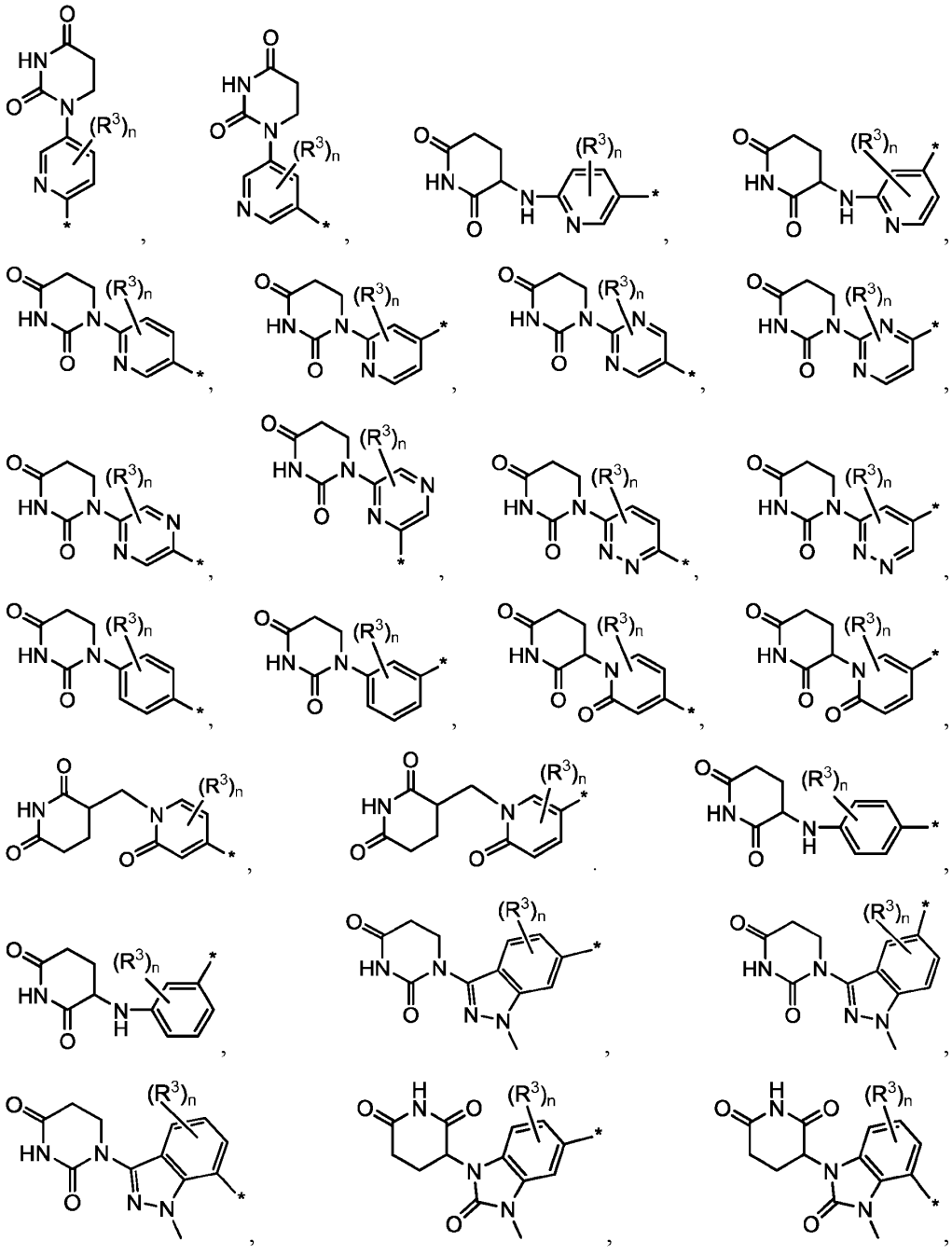
19. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein  is , , ,

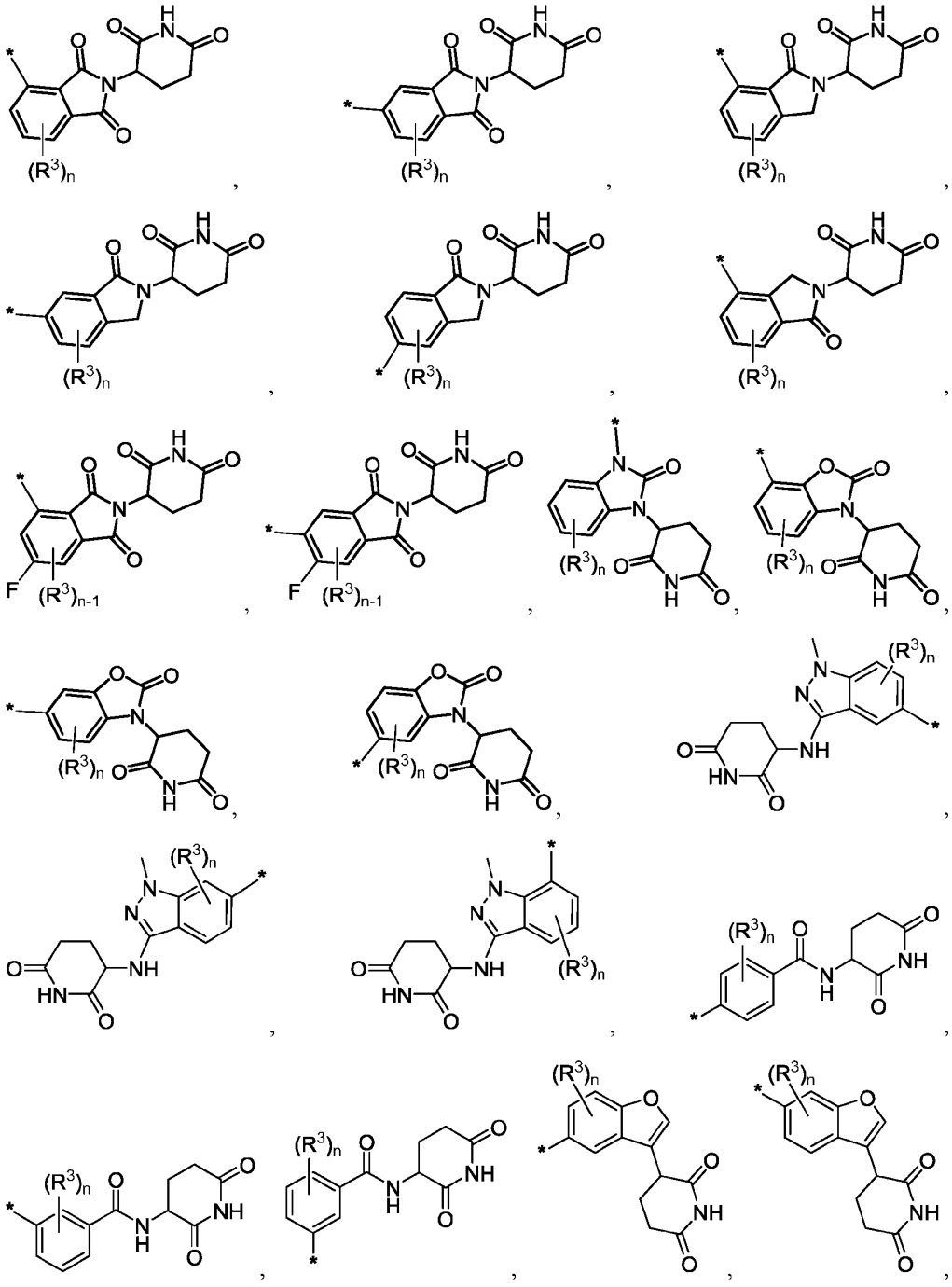
20. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein  is , , , , , , , , , , , , , or .

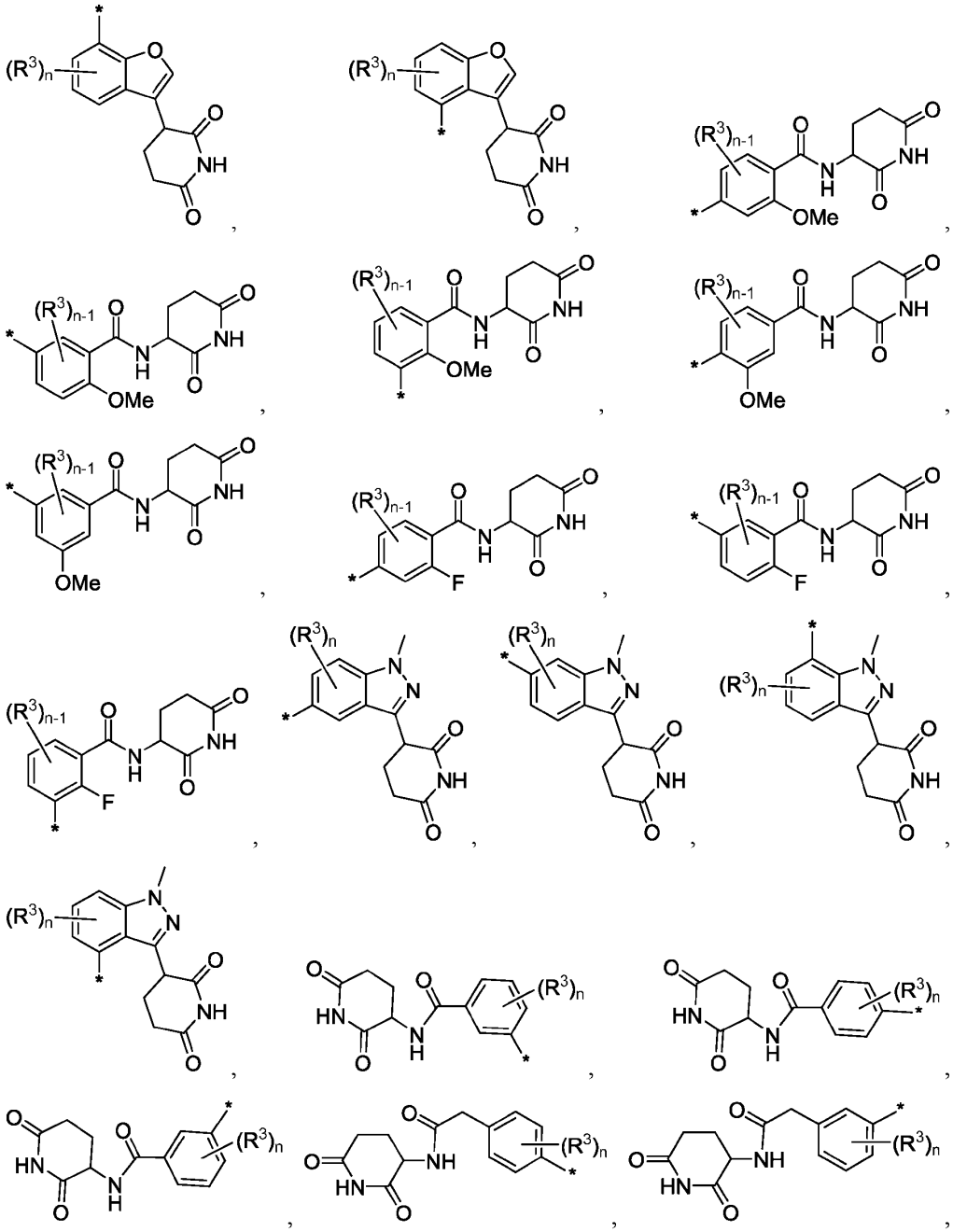
21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein  is ,

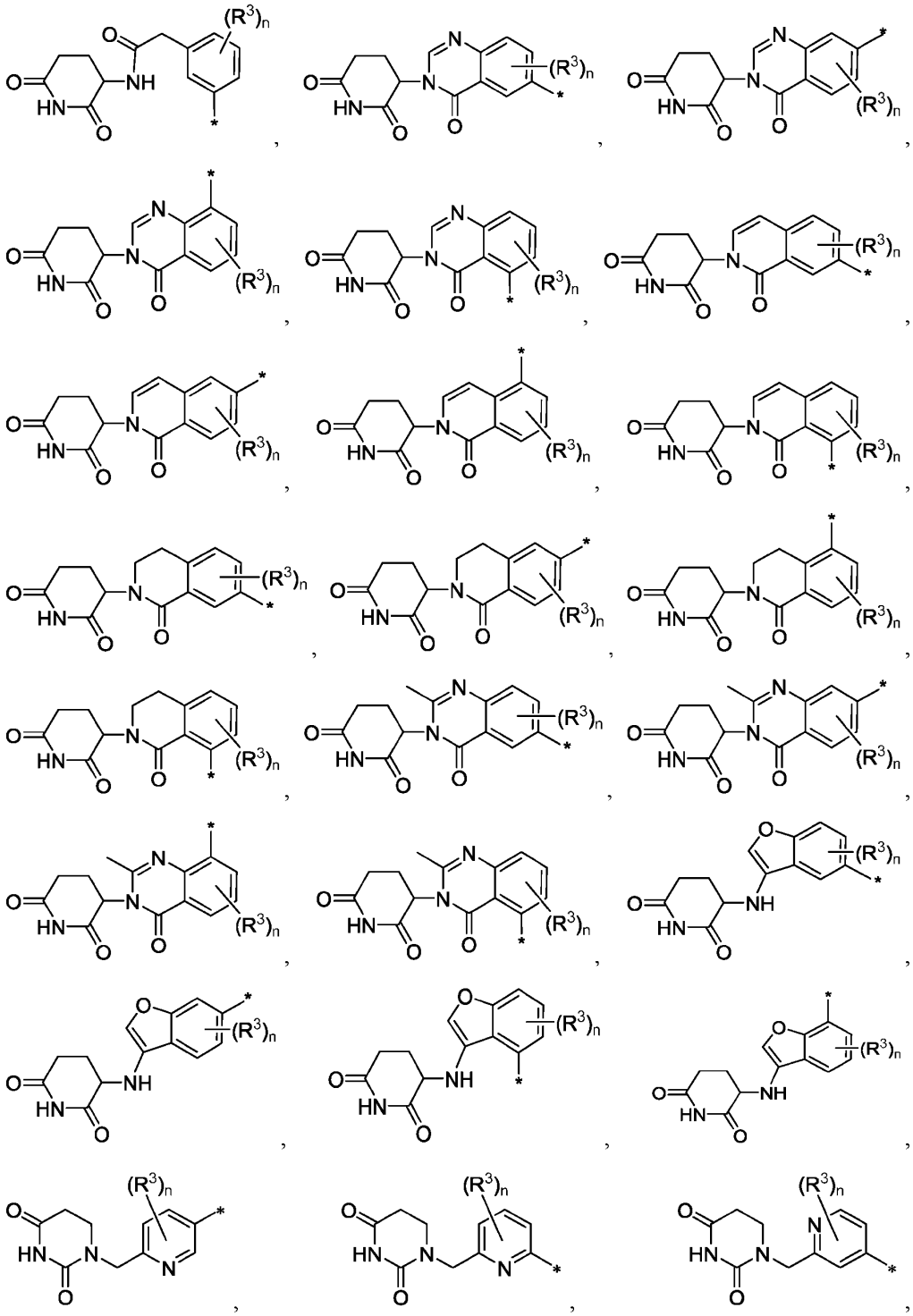

,

,

,

,

,

,

,

or

.

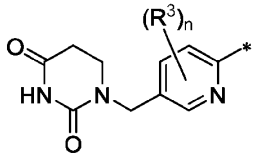
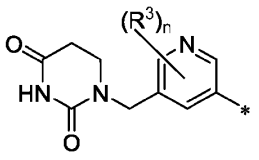
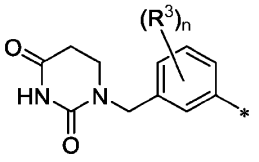
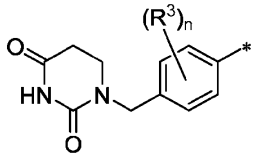
22. The compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein **L** is

,

,

,

,

,

,

,

,

,

,

,

,

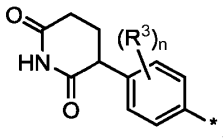
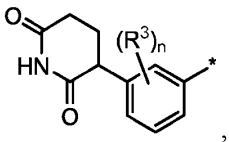
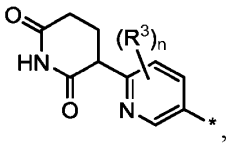
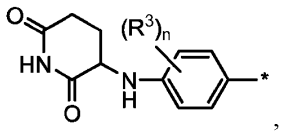
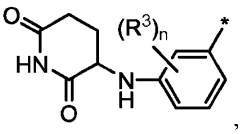
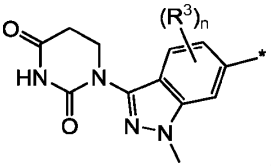
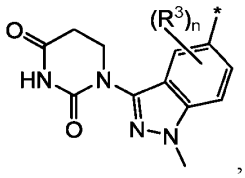
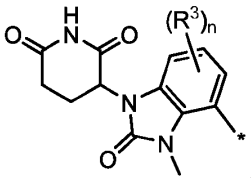
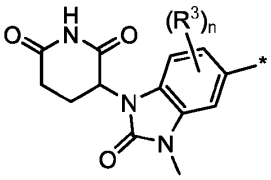
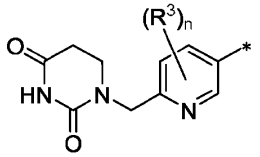


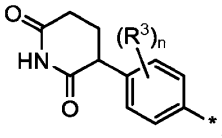
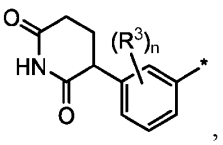
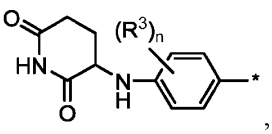


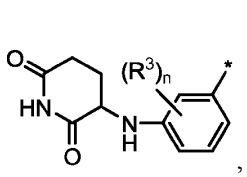
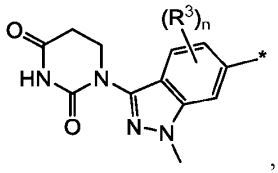
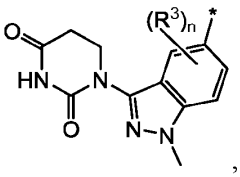
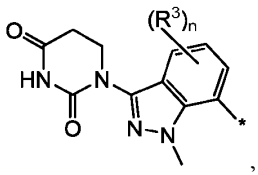
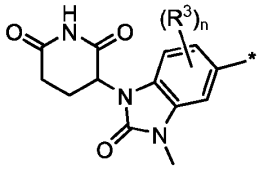
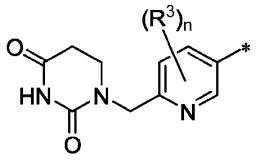







or


23. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein **L** is , , , , , , , , 
or


24. The compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, wherein **L** is , , ,


,

,

,

,

or

.

25. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^3}$ is F, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl or C_1-C_4 alkoxy.

26. The compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt thereof, wherein **n** is 0 or 1.

27. The compound of any one of claims 1 to 26, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^1}$ is an unsubstituted C_1-C_4 alkyl or a C_1-C_4 haloalkyl.

28. The compound of claim 27, or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^1}$ is ethyl.

29. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound has a structure selected from those of Compound Nos. 1 to 36 as listed in Table 1.

30. A pharmaceutical composition comprising an effective amount of the compound of any one of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient, or a combination thereof.

31. Use of a compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 30 in the manufacture of a medicament for ameliorating or treating a cancer, wherein the cancer is selected from a brain cancer, a cervicocerebral cancer, an esophageal cancer, a thyroid cancer, a small cell cancer, a non-small cell cancer, a breast cancer, a lung cancer, a stomach cancer, a gallbladder/bile duct cancer, a liver cancer, a pancreatic cancer, a colon cancer, a rectal cancer, an ovarian cancer, a choriocarcinoma, an uterus body cancer, an uterocervical cancer, a renal pelvis/ureter cancer, a bladder cancer, a prostate cancer, a penis cancer, a testicular cancer, a fetal cancer, Wilms' cancer, a skin cancer, malignant melanoma, a neuroblastoma, an

osteosarcoma, an Ewing's tumor, a soft part sarcoma, an acute leukemia, a chronic lymphatic leukemia, a chronic myelocytic leukemia, polycythemia vera, a malignant lymphoma, multiple myeloma, a Hodgkin's lymphoma and a non-Hodgkin's lymphoma.

32. Use of a compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 30 in the manufacture of a medicament for inhibiting replication of a malignant growth or a tumor, wherein the malignant growth or tumor is due to a cancer selected from a brain cancer, a cervicocerebral cancer, an esophageal cancer, a thyroid cancer, a small cell cancer, a non-small cell cancer, a breast cancer, a lung cancer, a stomach cancer, a gallbladder/bile duct cancer, a liver cancer, a pancreatic cancer, a colon cancer, a rectal cancer, an ovarian cancer, a choriocarcinoma, an uterus body cancer, an uterocervical cancer, a renal pelvis/ureter cancer, a bladder cancer, a prostate cancer, a penis cancer, a testicular cancer, a fetal cancer, Wilms' cancer, a skin cancer, malignant melanoma, a neuroblastoma, an osteosarcoma, an Ewing's tumor, a soft part sarcoma, an acute leukemia, a chronic lymphatic leukemia, a chronic myelocytic leukemia, polycythemia vera, a malignant lymphoma, multiple myeloma, a Hodgkin's lymphoma and a non-Hodgkin's lymphoma.

33. Use of a compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 30 in the manufacture of a medicament for ameliorating or treating a malignant growth or tumor, wherein the malignant growth or tumor is due to a cancer selected from a brain cancer, a cervicocerebral cancer, an esophageal cancer, a thyroid cancer, a small cell cancer, a non-small cell cancer, a breast cancer, a lung cancer, a stomach cancer, a gallbladder/bile duct cancer, a liver cancer, a pancreatic cancer, a colon cancer, a rectal cancer, an ovarian cancer, a choriocarcinoma, an uterus body cancer, an uterocervical cancer, a renal pelvis/ureter cancer, a bladder cancer, a prostate cancer, a penis cancer, a testicular cancer, a fetal cancer, Wilms' cancer, a skin cancer, malignant melanoma, a neuroblastoma, an osteosarcoma, an Ewing's tumor, a soft part sarcoma, an acute leukemia, a chronic lymphatic leukemia, a chronic myelocytic leukemia, polycythemia vera, a malignant lymphoma, multiple myeloma, a Hodgkin's lymphoma and a non-Hodgkin's lymphoma.