

COMPOSITIONS AND METHODS FOR DEGRADING ARYL HYDROCARBON RECEPTOR NUCLEAR TRANSLOCATOR PROTEIN

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of the priority of U.S. Provisional Application No. 63/617,634, filed January 4, 2024; the disclosure of which is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein are compounds for use in compositions and methods of degrading an aryl hydrocarbon receptor nuclear translocator protein (ARNT). Also provided are methods of treating, preventing, or ameliorating diseases and disorders in which ARNT activity is undesired.

BACKGROUND

[0003] ARNT (HIF-1 β) is a ~86 kDa protein encoded by the *ARNT* gene. ARNT contains a basic helix-loop-helix domain and two characteristic Per-Arnt-Sim (PAS) domains along with a PAC domain. The protein binds to a ligand-bound aryl hydrocarbon receptor (AhR) and aids in the movement of this complex to the nucleus, where it promotes the expression of genes involved in xenobiotic metabolism. ARNT is also a co-factor for transcriptional regulation by hypoxia-inducible factors (HIFs) *via* a heterodimer with, *e.g.*, HIF-1 α , HIF-2 α , and HIF-3 α . Chromosomal translocation of this locus with the ETV6 (ets variant 6) gene on chromosome 12 has been described in leukemias. Alternative splicing results in multiple transcript variants. ARNT also forms biologically relevant heterodimers with AHRR, NPAS1, NPAS3, NPAS4, SIM1, and SIM2. *See, e.g.*, Wu and Rastinejad, *Curr. Opin. Struct. Biol.* **2017**, 43, 1-9.

[0004] AhR is a ligand-activated transcription factor that mediates many of the responses to toxic environmental chemicals such as TCDD or dioxin-like polychlorinated biphenyls (PCBs). AhR must heterodimerize with ARNT to function as a transcription factor. After dimerization, the AhR:ARNT heterodimer induces the transcription of genes containing a xenobiotic response element (XRE) sequence in their promoter. It has also been shown that the AhR pathway is selectively active in indoleamine 2,3-dioxygenase 1 and tryptophan 2,3-dioxygenase 2 (IDO/TDO)-overexpressing tumors and is associated with resistance to immune checkpoint inhibitors. Selective AhR blockade delays progression in IDO/TDO-overexpressing tumors, and

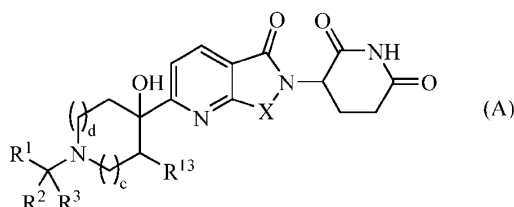
its efficacy is improved in combination with PD-1 blockade. *See, e.g., Campesato et al., Nat. Commun.* **2020**, *11*, 4011.

[0005] HIFs are a class of proteins that bind to ARNT to initiate hypoxia-induced gene expression. Elevated levels of two isoforms, HIF-1 α and HIF-2 α , are often found in malignant tumors and are thought to play a role in tumorigenesis and poor patient outcome. *See, e.g., Mandl et al., Cell Death Dis.* **2016**, 7, e2284. HIF-2 α is a pro-oncogenic factor in clear cell renal cell carcinoma and breast cancer. *See, e.g., Mazumder et al., Cancers (Basel)* **2023**, 15, 1316; de Heer et al., *J. Clin. Invest.* **2020**, 130, 5074-87; Chen et al., *Nature* **2016**, 539, 112-7; Kaelin, *J. Clin. Invest.* **2022**, 132, e162480. HIF-1 is also a key mediator in pathogenic immune responses, such as in lymphoid and myeloid immunomodulation in autoimmune diseases, controlling activation of macrophages, neutrophils and dendritic cells. *See, e.g., Islam et al., Immunology* **2021**, 164, 31-42; Taylor and Scholz, *Nat. Rev. Nephrol.* **2022**, 18, 573-87. HIF-2 α /ARNT has also been implicated in ischemic heart disease (IHD) pathogenesis. *See, e.g., Ullah et al., Biology (Basel)* **2023**, 12, 995.

[0006] Thus, ARNT plays a central role in AhR and HIF signaling. *See, e.g.,* Vorrink and Domann, *Chem. Biol. Interact.* **2014**, 218, 82-8. There is a need for compounds and compositions for use in methods of degrading ARNT, thereby mediating AhR and HIF signaling.

SUMMARY

[0007] Provided herein is a compound having the structure of Formula (A):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein:

R¹ is substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl;

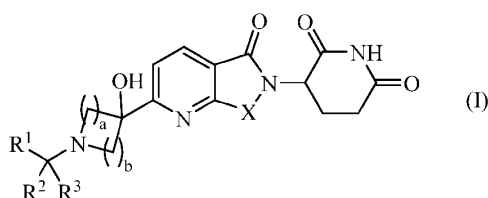
R² and R³ are each independently H, deuterium, substituted or unsubstituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₃-C₁₀ cycloalkyl; or R² and R³ together with the carbon atom to which they are attached form C(O) or substituted or unsubstituted C₃-C₁₀ cycloalkyl;

R¹³ is H, deuterium, or hydroxyl;

X is CR⁴R⁵ or C(O), wherein R⁴ and R⁵ are each independently H, deuterium, or substituted or unsubstituted C₁-C₁₀ alkyl; and

c and d are each independently an integer of 0, 1, or 2.

[0008] Also provided herein are compounds and compositions for degrading ARNT, wherein the compounds have the structure of Formula (I):



or a pharmaceutically acceptable derivative thereof, wherein:

R¹ is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R² and R³ are each independently H, alkyl, or cycloalkyl, or R² and R³ together form spirocycloalkyl;

a and b are each independently an integer from 1 to 3; and

X is CR⁴R⁵ or C(O), where R⁴ and R⁵ are each independently H, alkyl, or aralkyl.

[0009] Additionally provided herein is a pharmaceutical composition comprising a compound provided herein, *e.g.*, a compound of Formula (A) or (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; and a pharmaceutically acceptable excipient.

[0010] Furthermore, provided herein is a method of treating, preventing, or ameliorating one or more symptoms of an ARNT-mediated disease or disorder in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound provided herein, *e.g.*, a compound of Formula (A) or (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more

tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof.

[0011] Provided herein is a method of treating, preventing, or ameliorating one or more symptoms of cancer in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound provided herein, *e.g.*, a compound of Formula (A) or (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof.

[0012] Provided herein is a method of inhibiting the growth of a cell, comprising contacting the cell with an effective amount of a compound provided herein, *e.g.*, a compound of Formula (A) or (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof.

[0013] Provided herein is a method of inducing degradation of an ARNT, comprising contacting the ARNT with an effective amount of a compound provided herein, *e.g.*, a compound of Formula (A) or (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIG. 1 shows a dose-response plot for ARNT degradation using compound **A001** in NCI-H929 cells.

[0015] FIG. 2 shows a dose-response plot for ARNT degradation using (3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione) in NCI-H929 cells.

[0016] FIG. 3 shows a dose-response plot for helios degradation in a HiBiT assay at 24 h using compound **A001**.

[0017] FIG. 4 shows two dose-response plots for helios degradation in a HiBiT assay at 24 h using (3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione).

[0018] FIG. 5 shows a dose-response plot for helios degradation in a Jurkat cell line at 6 h using compound A001.

[0019] FIG. 6 shows a dose-response plot for helios degradation in a Jurkat cell line at 6 h using (3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione).

[0020] FIG. 7 shows a dose-response plot for VEGF inhibition using compound A001.

DETAILED DESCRIPTION

I. DEFINITIONS

[0021] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0022] 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 are incorporated herein by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0023] The singular forms "a," "an," and "the" include plural references, unless the context clearly dictates otherwise.

[0024] As used herein "subject" is an animal, such as a mammal, including human, such as a patient.

[0025] As used herein, a biological activity refers to the *in vivo* activities of a compound or physiological responses that result upon *in vivo* administration of a compound, composition, or other mixture. A biological activity, thus, encompasses therapeutic effects and pharmacokinetic behaviors of such a compound, composition, and mixture. Biological activities can be observed in an *in vitro* system designed to test for such activities.

[0026] As used herein, pharmaceutically acceptable derivatives of a compound include, but are not limited to, salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, clathrates, solvates, or hydrates thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to *N,N*-dibenzylethylene-diamine, chlorprocaine, choline, ammonia, diethanolamine, and other hydroxyalkylamines,

ethylene-diamine, *N*-methylglucamine, procaine, *N*-benzylphenethylamine, 1-parachlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as, but not limited to, lithium, potassium, and sodium; alkali earth metal salts, such as, but not limited to, barium, calcium, and magnesium; transition metal salts, such as, but not limited to, zinc; and inorganic salts, such as, but not limited to, sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as, but not limited to, hydrochlorides and sulfates; and salts of organic acids, such as, but not limited to, acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates, mesylates, and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids, and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula $-C=C(OR)$ where R is alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula $-C=C(OC(O)R)$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or 1 to about 2, 3, or 4, solvent or water molecules.

[0027] As used herein, treatment means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating diseases or disorders involving ARNT activity.

[0028] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the compound or pharmaceutical composition.

[0029] As used herein, and unless otherwise indicated, the terms "manage," "managing," and "management" encompass preventing the recurrence of the specified disease or disorder in a subject who has already suffered from the disease or disorder, and/or lengthening the time that a subject who has suffered from the disease or disorder remains in remission. The terms

encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a subject responds to the disease or disorder.

[0030] Where moieties are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical moieties that would result from writing the structure from right to left, *e.g.*, $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

[0031] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (*i.e.*, unbranched) or branched chain saturated hydrocarbon radical, which can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.*, C₁-C₁₀ means one to ten carbons). Examples of alkyl groups include, but are not limited to, groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *t*-butyl, isobutyl, *sec*-butyl, homologs and isomers of, for example, *n*-pentyl, *n*-hexyl, *n*-heptyl, and *n*-octyl.

[0032] The term "alkenyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (*i.e.*, unbranched) or branched chain hydrocarbon radical having one or more carbon-carbon double bonds, which can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.*, C₁-C₁₀ means one to ten carbons). Examples of alkenyl groups include, but are not limited to, vinyl (*i.e.*, ethenyl), 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), and the higher homologs and isomers.

[0033] The term "alkynyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (*i.e.*, unbranched) or branched chain hydrocarbon radical having one or more carbon-carbon triple bonds, which can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.*, C₁-C₁₀ means one to ten carbons). Examples of alkynyl groups include, but are not limited to, ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers.

[0034] The term "alkylene," by itself or as part of another substituent, means a divalent radical derived from an alkyl, as exemplified, but not limited, by $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, including those groups having 10 or fewer carbon atoms. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having six or fewer carbon atoms.

[0035] The terms "alkoxy," "alkylamino," and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule *via* an oxygen atom, an amino group, or a sulfur atom, respectively.

[0036] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, consisting of a heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atom may have an alkyl substituent to fulfill valency and/or may optionally be quaternized. The heteroatom(s) O, N, P, Si, and S may be placed at any interior position of the heteroalkyl group. Examples include, but are not limited to, $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, and $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ and $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$. Similarly, the term "heteroalkylene," by itself or as part of another substituent, means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C}(\text{O})_2\text{R}'-$ represents both $-\text{C}(\text{O})_2\text{R}'-$ and $-\text{R}'\text{C}(\text{O})_2-$.

[0037] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively, including bicyclic, tricyclic, and bridged bicyclic groups. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, norbornanyl, and bicyclo[2.2.2]octanyl. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, 1-azabicyclo[2.2.2]octanyl, and 2-azabicyclo[2.2.2]octanyl.

[0038] The terms "halo," by itself or as part of another substituent, means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C₁-C₄)alkyl" is meant to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, and 3-bromopropyl.

[0039] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent which can be a single ring or multiple rings (in one embodiment from 1 to 3 rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups that contain from one to four heteroatoms selected from N, O, and S in the ring(s), wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituent moieties for aryl and heteroaryl ring systems may be selected from the group of acceptable substituent moieties described herein. The term "heteroarylium" refers to a heteroaryl group that is positively charged on one or more of the heteroatoms.

[0040] The term "oxo" as used herein means an oxygen atom that is double bonded to a carbon atom.

[0041] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl," and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Non-limiting examples of substituent moieties for each type of radical are provided below.

[0042] Substituent moieties for alkyl, heteroalkyl, alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl groups are, in one embodiment, selected from, deuterium, $-OR'$, $=O$, $=NR'$, $=N-OR'$, $-NR'R''$, $-SR'$, halo, $-SiR'R''R'''$, $-OC(O)R'$, $-C(O)R'$, $-CO_2R'$, $-CONR'R''$, $-OC(O)NR'R''$, $-NR''C(O)R'$, $-NR'-C(O)NR''R'''$, $-NR''C(O)_2R'$, $-NR-C(NR'R''R''')=NR''''$, $-NR-C(NR'R'')=NR''''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R''$, $-NRSO_2R'$, $-NRSO_2NR'R''$, $-CN$, and $-NO_2$ in a number ranging from zero to the number of hydrogen atoms in such radical. In one embodiment, substituent moieties for cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl groups also include substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, and substituted and unsubstituted alkynyl. R' , R'' , R''' , and R'''' each in one embodiment independently are hydrogen,

substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (*e.g.*, aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound provided herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' groups when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituent moieties, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (*e.g.*, -CF₃ and -CH₂CF₃) and acyl (*e.g.*, -C(O)CH₃, -C(O)CF₃, and -C(O)CH₂OCH₃).

[0043] Substituent moieties for aryl and heteroaryl groups are, in one embodiment, selected from deuterium, halo, substituted and unsubstituted alkyl, substituted and unsubstituted alkenyl, and substituted and unsubstituted alkynyl, -OR', -NR'R'', -SR', -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'-C(O)NR''R''', -NR'C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN, -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of hydrogens on the aromatic ring system; and where R', R'', R''' and R'''' are, in one embodiment, independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound provided herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' groups when more than one of these groups is present.

[0044] Two of the substituent moieties on adjacent atoms of an aryl or heteroaryl ring may optionally form a ring of the formula -Q'-C(O)-(CRR')_q-Q'', wherein Q' and Q'' are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituent moieties on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'-, or a single bond,

and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituent moieties on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(CR''R''')_t-$, where s and t are independently integers of from 0 to 3, and X' is $-O-$, $-NR'-$, $-S-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituent moieties R , R' , R'' , and R''' are, in one embodiment, independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0045] As used herein, the term "heteroatom" or "ring heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0046] As used herein, a prodrug is a compound that, upon *in vivo* administration, is metabolized, or otherwise undergoes chemical changes under physiological conditions, by one or more steps or processes or otherwise converted to a biologically, pharmaceutically, or therapeutically active form of the compound. Additionally, prodrugs can be converted to a biologically, pharmaceutically, or therapeutically active form of the compound by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be converted to the compounds provided herein when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0047] Certain compounds provided herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds provided herein may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated herein and are intended to be within the scope of the present disclosure.

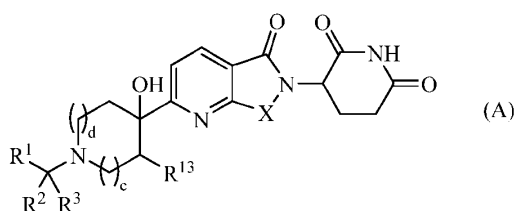
[0048] Certain compounds provided herein possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, tautomers, geometric isomers and individual isomers are encompassed within the scope of the present disclosure. The compounds provided herein do not include those which are known in the art to be too unstable to synthesize and/or isolate.

[0049] The compounds provided herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the

compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds provided herein, whether radioactive or not, are encompassed within the scope of the present disclosure.

II. COMPOUNDS FOR USE IN COMPOSITIONS AND METHODS

[0050] In one embodiment, provided herein is a compound having the structure of Formula (A):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein:

R¹ is substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl;

R² and R³ are each independently H, deuterium, substituted or unsubstituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₃-C₁₀ cycloalkyl; or R² and R³ together with the carbon atom to which they are attached form C(O) or substituted or unsubstituted C₃-C₁₀ cycloalkyl;

R¹³ is H, deuterium, or hydroxyl;

X is CR⁴R⁵ or C(O), wherein R⁴ and R⁵ are each independently H, deuterium, or substituted or unsubstituted C₁-C₁₀ alkyl; and

c and d are each independently an integer of 0, 1, or 2.

[0051] In another embodiment, provided herein is a compound for use in the compositions and methods provided herein having the structure of Formula (I):

$$\begin{array}{c}
 \text{O} \\
 \parallel \\
 \text{N} - \text{C} - \text{C} = \text{O} \\
 \parallel \quad \parallel \\
 \text{NH} \quad \text{O} \\
 \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{C} \\
 \parallel \quad \parallel \quad \parallel \quad \parallel \\
 \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \\
 \text{I}
 \end{array}$$

or a pharmaceutically acceptable derivative thereof, wherein:

R¹ is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R² and R³ are each independently H, alkyl, or cycloalkyl, or R² and R³ together form spirocycloalkyl;

a and b are each independently an integer from 1 to 3; and

X is CR⁴R⁵ or C(O), where R⁴ and R⁵ are each independently H, alkyl, or aralkyl.

[0052] In yet another embodiment, provided herein is a compound for use in the compositions and methods provided herein having the structure of Formula (Ia):

O=C1NC(=O)C2=C(N1)C(=O)N2C3=CC=C(C=C3)C(O)C4CCN(C4)C(R1)R2 (Ia)

or a pharmaceutically acceptable derivative thereof, wherein:

R¹ is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R² is H, alkyl or cycloalkyl; and

X is CR⁴R⁵ or C(O), where R⁴ and R⁵ are each independently H, alkyl, or aralkyl.

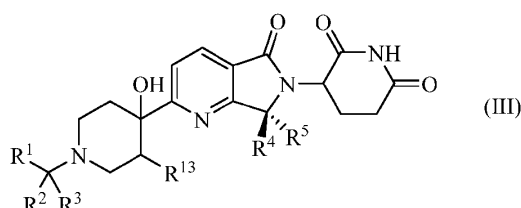
[0053] In certain embodiments, X is CR^4R^5 , wherein R^4 and R^5 are each as defined herein. In certain embodiments, X is C(O).

[0054] In yet another embodiment, provided herein is a compound having the structure of Formula (II):

O=C1NC(=O)C2=C(N1)c3ccc(cc3N2)[C@H](R4)(R5)C(C(O)CC(R13)N(C(C)(C)R2)(C(C)(C)R3)CC(R1)C(C)(C)R2)CC(C)(C)R13 (II)

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein R¹, R², R³, R⁴, R⁵, R¹³, c, and d are each as defined herein.

[0055] In yet another embodiment, provided herein is a compound having the structure of Formula (III):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein R¹, R², R³, R⁴, R⁵, and R¹³ are each as defined herein.

[0056] In certain embodiments, R¹ is aryl or heteroaryl, each optionally substituted with -OR⁶, -NR⁷R⁸, -(CH₂)_n-R⁹, -C(O)NR⁷R⁸, -NR⁷C(O)R¹², -S(O)_pNR⁷R⁸, -NR⁷S(O)_pR¹², -C(O)-(CH₂)_m-R¹⁰, or -S(O)_p-(CH₂)_q-R¹¹, where R⁶ is H, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; R⁷ and R⁸ are each independently H, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or R⁷ and R⁸ together with the atom(s) to which they are attached form heterocycloalkyl; R⁹, R¹⁰, and R¹¹ are each independently monocyclic or fused, bridged, or spiro bicyclic cycloalkyl or monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; R¹² is alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and m, n, p, and q are each independently an integer from 0 to 2; or R¹ is aryl or heteroaryl, each optionally fused to a cycloalkyl or heterocycloalkyl ring.

[0057] In certain embodiments, R¹ is aryl or heteroaryl, each optionally substituted with -OR⁶, -NR⁷R⁸, -(CH₂)_n-R⁹, -C(O)NR⁷R⁸, -NR⁷C(O)R¹², -S(O)_pNR⁷R⁸, -NR⁷S(O)_pR¹², -C(O)-(CH₂)_m-R¹⁰, or -S(O)_p-(CH₂)_q-R¹¹; where R⁶ is H, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; R⁷ and R⁸ are each independently H, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or R⁷ and R⁸ together with the atom(s) to which they are attached form heterocycloalkyl; R⁹, R¹⁰, and R¹¹ are each independently monocyclic or fused, bridged, or spiro bicyclic

cycloalkyl or monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; R^{12} is alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and m, n, p, and q are each independently an integer from 0 to 2.

[0058] In certain embodiments, R^1 is aryl, optionally substituted with $-OR^6$, $-NR^7R^8$, $-(CH_2)_n-R^9$, $-C(O)NR^7R^8$, $-NR^7C(O)R^{12}$, $-S(O)_pNR^7R^8$, $-NR^7S(O)_pR^{12}$, $-C(O)-R^{10}$, or $-S(O)_2-R^{11}$; where R^6 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; R^7 and R^8 are each independently H, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or R^7 and R^8 together with the atom(s) to which they are attached form heterocycloalkyl; R^9 , R^{10} , and R^{11} are each independently monocyclic or fused, bridged, or spiro bicyclic cycloalkyl or monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; R^{12} is alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and n and p are each independently an integer from 0 to 2.

[0059] In certain embodiments, R^1 is aryl, optionally substituted with $-OR^6$, $-NR^7R^8$, $-(CH_2)_n-R^9$, $-C(O)NR^7R^8$, $-NR^7C(O)R^{12}$, $-S(O)_pNR^7R^8$, $-NR^7S(O)_pR^{12}$, $-C(O)-R^{10}$, or $-S(O)_2-R^{11}$; where R^6 is heterocycloalkyl or aryl; R^7 is H; R^8 is heterocycloalkyl or aryl; R^9 , R^{10} and R^{11} are each independently monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; R^{12} is alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; n is an integer of 0 or 1; and p is each independently an integer from 0 to 2.

[0060] In a certain embodiments, R^1 is aryl, optionally substituted with $-OR^6$, $-NR^7R^8$, $-(CH_2)_n-R^9$, $-C(O)-R^{10}$, or $-S(O)_2-R^{11}$; where R^6 is heterocycloalkyl or aryl; R^7 is H; R^8 is heterocycloalkyl or aryl; R^9 , R^{10} and R^{11} are each independently monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; and n is an integer of 0 or 1.

[0061] In certain embodiments, R^1 is phenyl, optionally substituted as described herein.

[0062] In certain embodiments, R^1 is phenyl, optionally substituted with $-OR^6$, $-NR^7R^8$, $-(CH_2)_n-R^9$, $-C(O)NR^7R^8$, $-NR^7C(O)R^8$, $-C(O)-R^{10}$, or $-S(O)_2-R^{11}$; where R^6 is heterocycloalkyl or aryl; R^7 is H; R^8 is heterocycloalkyl or aryl; R^9 , R^{10} , and R^{11} are each independently monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; and n is an integer of 0 or 1.

[0063] In certain embodiments, R^1 is unsubstituted phenyl.

[0064] In certain embodiments, R^1 is aryl, optionally fused to a cycloalkyl or heterocycloalkyl ring. In certain embodiments, R^1 is phenyl, optionally fused to a heterocycloalkyl ring.

[0065] In certain embodiments, R^1 is C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, C_6 - C_{14} aryl, C_7 - C_{15} arylalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with one, two, three, or

four substituents, each of which is independently deuterium, cyano, halo, nitro, oxo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CO₂R', -CONR'R'', -OR', -OC(O)R', -OC(O)NR'R'', -NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NR'C(O)NR''R''', -NRSO₂R', -NRSO₂NR'R'', -SR', -S(O)R', -S(O)₂R', or -S(O)₂NR'R''; wherein each R', R'', and R''' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl; or R' and R'' together with the nitrogen atom to which they are attached form substituted or unsubstituted C₃-C₁₀ cycloalkyl, or substituted or unsubstituted heterocycloalkyl.

[0066] In certain embodiments, R¹ is C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₇-C₁₅ arylalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted with one or more substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0067] In certain embodiments, R¹ is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R¹ is C₁-C₁₀ alkyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'',

–OR', –NR'R", –S(O)₂R', or –S(O)₂NR'R"; wherein each R' and R" is independently hydrogen, substituted or unsubstituted C₁–C₁₀ alkyl, substituted or unsubstituted C₁–C₁₀ heteroalkyl, substituted or unsubstituted C₁–C₁₀ cycloalkyl, substituted or unsubstituted C₆–C₁₄ aryl, substituted or unsubstituted C₇–C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R¹ is isopropyl.

[0068] In certain embodiments, R¹ is substituted or unsubstituted C₃–C₁₀ cycloalkyl. In certain embodiments, R¹ is C₃–C₁₀ cycloalkyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted C₁–C₁₀ alkyl, substituted or unsubstituted C₁–C₁₀ heteroalkyl, substituted or unsubstituted C₃–C₁₀ cycloalkyl, substituted or unsubstituted C₆–C₁₄ aryl, substituted or unsubstituted C₇–C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, –COR', –CONR'R", –OR', –NR'R", –S(O)₂R', or –S(O)₂NR'R"; wherein each R' and R" is independently hydrogen, substituted or unsubstituted C₁–C₁₀ alkyl, substituted or unsubstituted C₁–C₁₀ heteroalkyl, substituted or unsubstituted C₁–C₁₀ cycloalkyl, substituted or unsubstituted C₆–C₁₄ aryl, substituted or unsubstituted C₇–C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0069] In certain embodiments, R¹ is substituted or unsubstituted monocyclic C₃–C₁₀ cycloalkyl. In certain embodiments, R¹ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, each optionally substituted. In certain embodiments, R¹ is substituted or unsubstituted cyclohexyl.

[0070] In certain embodiments, R¹ is substituted or unsubstituted bicyclic C₃–C₁₀ cycloalkyl. In certain embodiments, R¹ is bridged, fused, or spiro C₄–C₁₀ cycloalkyl, each optionally substituted. In certain embodiments, R¹ is substituted or unsubstituted bridged C₅–C₁₀ cycloalkyl. In certain embodiments, R¹ is substituted or unsubstituted bicyclo[1.1.1]pentanyl. In certain embodiments, R¹ is substituted or unsubstituted bicyclo[1.1.1]pentan-1-yl. In certain embodiments, R¹ is substituted or unsubstituted fused C₄–C₁₀ cycloalkyl. In certain embodiments, R¹ is substituted or unsubstituted spiro C₄–C₁₀ cycloalkyl. In certain embodiments, R¹ is cyclohexyl, 4-aminocyclohexyl, or 3-fluorobicyclo[1.1.1]pentan-1-yl.

[0071] In certain embodiments, R¹ is substituted or unsubstituted C₆–C₁₄ aryl. In certain embodiments, R¹ is C₆–C₁₄ aryl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁–C₁₀ alkyl,

substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0072] In certain embodiments, R¹ is substituted or unsubstituted phenyl. In certain embodiments, R¹ is phenyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R¹ is phenyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, or -OR'; wherein R' is substituted or unsubstituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₆-C₁₄ aryl.

[0073] In certain embodiments, R¹ is phenyl, optionally substituted one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanymethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidiny, difluoropiperidiny, (hydroxymethyl)piperidiny, hydroxypiperidiny, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxy-ethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyloxy, amino, dimethyl-

amino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R¹ is phenyl, optionally substituted one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, morpholinomethyl, methoxymethyl, phenoxy-methyl, phenyl, pyrazolyl, methylpyrazolyl, piperidinyl, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

[0074] In certain embodiments, R¹ is phenyl, optionally substituted one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxy-methyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R¹ is phenyl, optionally substituted one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, morpholinomethyl, methoxymethyl, phenoxy-methyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, or phenoxy.

[0075] In certain embodiments, R¹ is phenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 3-(1,1-difluoroethyl)phenyl, 4-(1,1-difluoroethyl)phenyl, 3-isopropylphenyl, 4-isopropylphenyl, 3-*tert*-butylphenyl, 4-*tert*-butylphenyl, 4-(oxan-4-ylmethyl)phenyl, 4-(morpholinomethyl)phenyl, 4-hydroxymethylphenyl, 4-methoxymethylphenyl, 4-phenoxy-methylphenyl, 4-((dimethylamino)methyl)phenyl, 4-chloro-3-fluorophenyl, 4-chloro-3-methylphenyl, 3,4-di(trifluoromethyl)phenyl, 3-cyclobutylphenyl, 4-cyclobutylphenyl, 4-cyclohexylphenyl, 4-phenylphenyl, 4-pyrazol-1-ylphenyl, 4-(1-methylpyrazol-3-yl)phenyl, 4-(1-methylpyrazol-4-yl)phenyl, 4-(2-methylpyrazol-3-yl)phenyl, 3-(oxetan-3-yl)phenyl, 4-(oxetan-3-yl)phenyl, 3-oxan-4-ylphenyl, 4-oxan-4-ylphenyl, 3-(piperidin-1-yl)phenyl, 4-

(piperidin-1-yl)phenyl, 4-(4,4-difluoropiperidin-1-yl)phenyl, 4-(4-(hydroxymethyl)piperidin-1-yl)phenyl, 4-(4-hydroxypiperidin-1-yl)phenyl, 3-morpholinophenyl, 4-morpholinophenyl, 3-(8-azabicyclo[3.2.1]octan-8-yl)phenyl, 4-(8-azabicyclo[3.2.1]octan-8-yl)phenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-trifluoromethoxyphenyl, 4-(2-hydroxyethoxy)phenyl, 3-phenoxyphenyl, 4-phenoxyphenyl, 4-benzoxyphephenyl, 4-(piperidin-4-yloxy)-phenyl, 4-(oxan-4-yl)oxyphenyl, 3,4-dimethoxyphenyl, 3-aminophenyl, 3-dimethylaminophenyl, 4-dimethylaminophenyl, 4-phenylaminophenyl, 3-amino-carbonylphenyl, 4-aminocarbonylphenyl, 3-methylaminocarbonylphenyl, 4-methylamino-carbonylphenyl, 4-dimethylaminocarbonylphenyl, 4-(methylsulfonyl)phenyl, or 4-amino-sulfonylphenyl.

[0076] In certain embodiments, R¹ is phenyl, 3-cyanophenyl, 4-cyanophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-methylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-ethylphenyl, 3-(1,1-difluoroethyl)phenyl, 4-(1,1-difluoroethyl)phenyl, 4-isopropylphenyl, 4-*tert*-butylphenyl, 4-(oxan-4-ylmethyl)phenyl, 4-methoxymethylphenyl, 4-phenylphenyl, 4-pyrazol-1-ylphenyl, 4-(1-methylpyrazol-3-yl)phenyl, 4-(1-methylpyrazol-4-yl)phenyl, 4-(piperidin-1-yl)phenyl, 3-morpholinophenyl, 3-(8-azabicyclo[3.2.1]octan-8-yl)phenyl, 4-(8-azabicyclo[3.2.1]octan-8-yl)phenyl, 3-phenoxyphenyl, or 4-phenoxyphenyl.

[0077] In certain embodiments, R¹ is substituted or unsubstituted bicyclic C₈-C₁₄ aryl. In certain embodiments, R¹ is bicyclic C₈-C₁₄ aryl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R"; wherein each R' and R" is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R¹ is substituted or unsubstituted 2,3-dihydroindenyl. In certain embodiments, R¹ is substituted or unsubstituted 2,3-dihydroinden-2-yl.

[0078] In certain embodiments, R¹ is substituted or unsubstituted C₇-C₁₅ arylalkyl. In certain embodiments, R¹ is C₇-C₁₅ arylalkyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R¹ is substituted or unsubstituted benzyl. In certain embodiments, R¹ is benzyl or 3-fluorobenzyl.

[0079] In certain embodiments, R¹ is substituted or unsubstituted heteroaryl. In certain embodiments, R¹ is heteroaryl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0080] In certain embodiments, R¹ is substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R¹ is 5- or 6-membered heteroaryl, each optionally substituted. In certain embodiments, R¹ is substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R¹ is 5-membered heteroaryl, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or

$-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ heteroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl, substituted or unsubstituted $\text{C}_7\text{-C}_{15}$ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^1 is isoxazolyl, oxazolyl, pyrazolyl, thiazolyl, 1,2,4-triazolyl, 1,3,4-thiadiazolyl, or tetrazolyl, each optionally one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl. In certain embodiments, R^1 is isoxazol-4-yl, oxazol-2-yl, pyrazol-3-yl, pyrazol-4-yl, thiazol-2-yl, 1,2,4-triazol-3-yl, 1,3,4-thiadiazol-2-yl, or tetrazol-5-yl, each optionally one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl. In certain embodiments, R^1 is isoxazol-4-yl, oxazol-2-yl, pyrazol-4-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 3-methylpyrazol-4-yl, 1-(trifluoromethyl)pyrazol-4-yl, 1-(isopropyl)pyrazol-3-yl, 1-(isopropyl)pyrazol-4-yl, 1-phenyl-pyrazol-4-yl, thiazol-2-yl, 5-methylthiazol-2-yl, 1,2,4-triazol-3-yl, 5-methyl-1,3,4-thiadiazol-2-yl, or tetrazol-5-yl.

[0081] In certain embodiments, R^1 is substituted or unsubstituted 6-membered heteroaryl. In certain embodiments, R^1 is 6-membered heteroaryl, each of which is independently deuterium, cyano, halo, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ heteroalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl, substituted or unsubstituted $\text{C}_7\text{-C}_{15}$ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ heteroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl, substituted or unsubstituted $\text{C}_7\text{-C}_{15}$ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^1 is pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each optionally one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl. In certain embodiments, R^1 is pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 2-hydroxypyridin-4-yl, or 1-methyl-2-oxo-1,2-dihydropyridin-4-yl.

[0082] In certain embodiments, R^1 is substituted or unsubstituted bicyclic heteroaryl. In certain embodiments, R^1 is 5,5-, 5,6-, or 6,6-fused heteroaryl, each optionally substituted. In certain embodiments, R^1 is substituted or unsubstituted 5,5-fused heteroaryl. In certain

embodiments, R¹ is 5,5-fused heteroaryl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R¹ is 5,6-dihydro-cyclopenta[*d*]thiazolyl or 6,7-dihydropyrrolo[1,2-*a*]imidazolyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl. In certain embodiments, R¹ is 5,6-dihydrocyclopenta[*d*]-thiazol-2-yl or 6,7-dihydropyrrolo[1,2-*a*]imidazol-2-yl.

[0083] In certain embodiments, R¹ is substituted or unsubstituted 5,6-fused heteroaryl. In certain embodiments, R¹ is 5,6-fused heteroaryl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R¹ is benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzo[*d*][1,2,3]triazolyl, imidazo[1,2-*a*]-pyridinyl, indolyl, indazolyl, pyrazolo[1,5-*a*]pyridinyl, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[3,2-*b*]-pyridinyl, or [1,2,4]triazolo[1,5-*a*]pyridinyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl. In certain embodiments, R¹ is benzofuran-6-yl, benzimidazol-5-yl, benzoxazol-2-yl, benzothiazol-2-yl, benzo[*d*]-[1,2,3]triazol-5-yl, imidazo[1,2-*a*]pyridin-2-yl,

indol-5-yl, indol-6-yl, indazol-4-yl, indazol-5-yl, indazol-6-yl, pyrazolo[1,5-*a*]pyridin-6-yl, pyrrolo[2,3-*b*]pyridin-5-yl, pyrrolo[3,2-*b*]pyridin-2-yl, pyrrolo[3,2-*b*]pyridin-6-yl, or [1,2,4]triazolo[1,5-*a*]pyridin-7-yl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl.

[0084] In certain embodiments, R¹ is 2,3-dihydroisoindolyl, 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl, benzo[*d*][1,3]dioxolyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridinyl, or 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridinyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl. In certain embodiments, R¹ is 2,3-dihydroisoindol-5-yl, 2,3-dihydrobenzo-furan-5-yl, 2,3-dihydrobenzofuran-6-yl, 1,3-dihydroisobenzofuran-5-yl, benzo[*d*]-[1,3]dioxol-5-yl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl, or 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridin-3-yl, each optionally substituted with one or two substituents, each of which is independently oxo, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl.

[0085] In certain embodiments, R¹ is benzofuran-6-yl, 1-methylbenzimidazol-5-yl, 3-methylbenzimidazol-5-yl, benzoxazol-2-yl, benzothiazol-2-yl, 1-methylbenzo[*d*][1,2,3]triazol-5-yl, imidazo[1,2-*a*]pyridin-2-yl, 1-methylindol-5-yl, 1-methylindol-6-yl, indazol-5-yl, 1-methylindazol-4-yl, 1-methylindazol-5-yl, 1-methylindazol-6-yl, pyrazolo[1,5-*a*]pyridin-6-yl, 2,2-difluorobenzo[*d*][1,3]dioxol-5-yl, pyrrolo[2,3-*b*]pyridin-5-yl, pyrrolo[3,2-*b*]pyridin-2-yl, pyrrolo[3,2-*b*]pyridin-6-yl, 2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl, 2,2-dimethyl-2,3-dihydrobenzofuran-6-yl, [1,2,4]triazolo[1,5-*a*]pyridin-7-yl, 1,3-dihydroisobenzofuran-5-yl, 2,3-dihydrobenzofuran-5-yl, 3-oxo-3,4-dihydro-1,4-benzoxazin-6-yl, 2,3-dihydroinden-2-yl, 2,3-dihydroisoindol-5-yl, 3-oxo-2,3-dihydroisoindol-5-yl, 2,3-dihydrobenzofuran-6-yl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl, or 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridin-3-yl.

[0086] In certain embodiments, R¹ is substituted or unsubstituted 6,6-fused heteroaryl. In certain embodiments, R¹ is 6,6-fused heteroaryl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently

hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R¹ is quinolinyl, chromanyl, 3,4-dihydropyrido[3,2-*b*][1,4]oxazinyl, or 3,4-dihydro-1,4-benzoxazinyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl. In certain embodiments, R¹ is quinolin-2-yl, quinolin-3-yl, quinolin-6-yl, chroman-6-yl, chroman-7-yl, 3,4-dihydropyrido[3,2-*b*][1,4]oxazin-7-yl, or 3,4-dihydro-1,4-benzoxazin-6-yl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl. In certain embodiments, R¹ is quinolin-2-yl, quinolin-3-yl, quinolin-6-yl, chroman-6-yl, chroman-7-yl, 4-methyl-3,4-dihydropyrido[3,2-*b*][1,4]oxazin-7-yl, or 3-oxo-3,4-dihydro-1,4-benzoxazin-6-yl.

[0087] In certain embodiments, R¹ is substituted or unsubstituted heterocycloalkyl. In certain embodiments, R¹ is heterocycloalkyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R'', wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0088] In certain embodiments, R¹ is substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R¹ is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted. In certain embodiments, R¹ is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl,

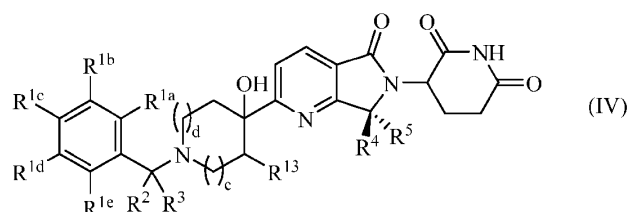
substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ heteroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl, substituted or unsubstituted $\text{C}_7\text{-C}_{15}$ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0089] In certain embodiments, R^1 is substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^1 is 6-membered heterocycloalkyl, each optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ heteroalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl, substituted or unsubstituted $\text{C}_7\text{-C}_{15}$ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ heteroalkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl, substituted or unsubstituted $\text{C}_7\text{-C}_{15}$ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0090] In certain embodiments, R^1 is azetidiny, oxanyl, piperidiny, tetrahydrothiopyranyl, 2-azaspiro[3.3]heptanyl, 2-azaspiro[3.5]nonanyl, 3-azaspiro[5.5]undecanyl, or 8-azabicyclo[3.2.1]octanyl, each optionally substituted with one or two substituents, each of which is independently oxo, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, phenyl, or pyridiny. In certain embodiments, R^1 is azetidin-3-yl, oxan-2-yl, oxan-3-yl, piperidin-3-yl, piperidin-4-yl, tetrahydrothiopyran-4-yl, 2-azaspiro[3.3]heptan-6-yl, 2-azaspiro[3.5]nonan-7-yl, 3-azaspiro[5.5]undecan-9-yl, or 8-azabicyclo[3.2.1]octan-3-yl, each optionally substituted with one or two substituents, each of which is independently oxo, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl. In certain embodiments, R^1 is 1-phenylazetidin-3-yl, oxan-2-yl, oxan-3-yl, piperidin-4-yl, 1-(isopropyl)piperidin-4-yl, 1-phenylpiperidin-3-yl, 1-phenylpiperidin-4-yl, 1-(2-chlorophenyl)piperidin-4-yl, 1-(3-chlorophenyl)piperidin-4-yl, 1-(4-chlorophenyl)piperidin-4-yl, 1-benzylpiperidin-4-yl, 1-(pyridin-3-yl)piperidin-4-yl, 1-(pyridin-2-yl)piperidin-4-yl, 1-acetylpiperidin-4-yl, 1,1-dioxido-tetrahydrothiopyran-4-yl, 2-azaspiro[3.3]heptan-6-yl, 2-azaspiro[3.5]nonan-7-yl, 8-phenyl-8-azabicyclo[3.2.1]octan-3-yl, or 3-azaspiro[5.5]undecan-9-yl. In certain embodiments, R^1 is 1-

phenylpiperidin-3-yl, 1-phenylpiperidin-4-yl, 1-(3-chlorophenyl)piperidin-4-yl, or 1-(4-chlorophenyl)piperidin-4-yl.

[0091] In yet another embodiment, provided herein is a compound having the structure of Formula (IV):

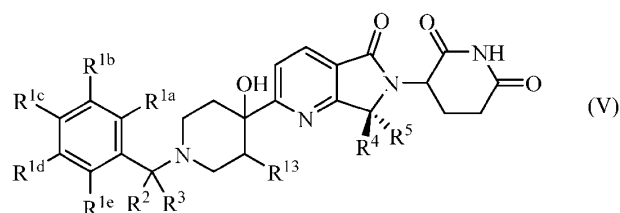


or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, or a pharmaceutically acceptable derivative thereof, wherein:

R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently H, deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl; or R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl; or R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl; and

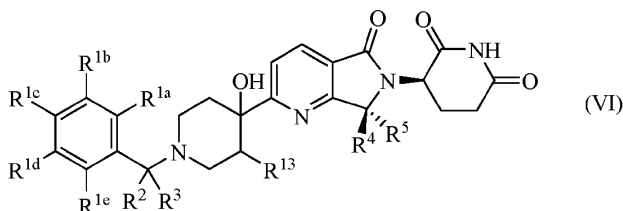
R², R³, R⁴, R⁵, R¹³, c, and d are each as defined herein.

[0092] In yet another embodiment, provided herein is a compound having the structure of Formula (V):



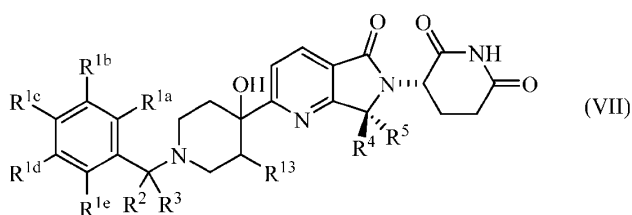
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein R², R³, R⁴, R⁵, R¹³, R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each as defined herein.

[0093] In yet another embodiment, provided herein is a compound having the structure of Formula (VI):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein R², R³, R⁴, R⁵, R¹³, R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each as defined herein.

[0094] In yet another embodiment, provided herein is a compound having the structure of Formula (VII):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein R², R³, R⁴, R⁵, R¹³, R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each as defined herein.

[0095] In certain embodiments, R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently H, deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0096] In certain embodiments, R^{1a} is H, deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0097] In certain embodiments, R^{1a} is H. In certain embodiments, R^{1a} is deuterium. In certain embodiments, R^{1a} is cyano. In certain embodiments, R^{1a} is halo. In certain embodiments, R^{1a} is fluoro or chloro. In certain embodiments, R^{1a} is fluoro. In certain embodiments, R^{1a} is chloro. In certain embodiments, R^{1a} is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1a} is methyl, ethyl, propyl, or butyl, each optionally substituted. In certain embodiments, R^{1a} is methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, or dimethylaminomethyl. In certain embodiments, R^{1a} is methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxy-methyl, or dimethylaminomethyl. In certain embodiments, R^{1a} is substituted or unsubstituted C₁-C₁₀ heteroalkyl.

[0098] In certain embodiments, R^{1a} is substituted or unsubstituted C₃-C₁₀ cycloalkyl. In certain embodiments, R^{1a} cyclobutyl or cyclohexyl, each optionally substituted. In certain

embodiments, R^{1a} is substituted or unsubstituted C₆-C₁₄ aryl. In certain embodiments, R^{1a} is substituted or unsubstituted phenyl. In certain embodiments, R^{1a} is substituted or unsubstituted C₇-C₁₅ arylalkyl. In certain embodiments, R^{1a} is substituted or unsubstituted heteroaryl. In certain embodiments, R^{1a} is substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{1a} is 5- or 6-membered heteroaryl, each optionally substituted. In certain embodiments, R^{1a} is substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{1a} is substituted or unsubstituted pyrazolyl. In certain embodiments, R^{1a} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted. In certain embodiments, R^{1a} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted with substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1a} is pyrazol-1-yl, 1-methylpyrazol-3-yl, 2-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{1a} is pyrazol-1-yl, 1-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{1a} is substituted or unsubstituted 6-membered heteroaryl.

[0099] In certain embodiments, R^{1a} is substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{1a} is substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{1a} is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted. In certain embodiments, R^{1a} is substituted or unsubstituted 3-membered heterocycloalkyl. In certain embodiments, R^{1a} is substituted or unsubstituted 4-membered heterocycloalkyl. In certain embodiments, R^{1a} is substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{1a} is substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{1a} is substituted or unsubstituted 7-membered heterocycloalkyl. In certain embodiments, R^{1a} is oxetanyl, oxanyl, piperidiny, or morpholino, each optionally substituted. In certain embodiments, R^{1a} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, or morpholino, each optionally substituted. In certain embodiments, R^{1a} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, or morpholino. In certain embodiments, R^{1a} is piperidin-1-yl or morpholino.

[0100] In certain embodiments, R^{1a} is substituted or unsubstituted bicyclic heterocycloalkyl. In certain embodiments, R^{1a} is bridged, fused, or spiro heterocycloalkyl, each optionally substituted. In certain embodiments, R^{1a} is substituted or unsubstituted bridged heterocycloalkyl. In certain embodiments, R^{1a} is substituted or unsubstituted 8-azabicyclo[3.2.1]octanyl. In certain embodiments, R^{1a} is substituted or unsubstituted 8-azabicyclo[3.2.1]octan-8-yl. In certain

embodiments, R^{1a} is substituted or unsubstituted fused heterocycloalkyl. In certain embodiments, R^{1a} is substituted or unsubstituted heterocycloalkyl.

[0101] In certain embodiments, R^{1a} is $-\text{COR}'$, wherein R' is as defined herein. In certain embodiments, R^{1a} is $-\text{COR}'$, wherein R' is substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{1a} is $-\text{CONR}'\text{R}''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{1a} is $-\text{CONR}'\text{R}''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{1a} is $-\text{OR}'$, wherein R' is as defined herein. In certain embodiments, R^{1a} is $-\text{OR}'$, wherein R' is independently H, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, or substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl. In certain embodiments, R^{1a} is $-\text{NR}'\text{R}''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{1a} is $-\text{NR}'\text{R}''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{1a} is $-\text{S}(\text{O})_2\text{R}'$, wherein R' is as defined herein. In certain embodiments, R^{1a} is $-\text{S}(\text{O})_2\text{R}'$, wherein R' is substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{1a} is $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein R' and R'' are each as defined herein. In certain embodiments, R^{1a} is $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl.

[0102] In certain embodiments, R^{1a} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidiny, difluoropiperidiny, (hydroxymethyl)piperidiny, hydroxypiperidiny, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzyloxy, oxanyloxy, piperidinyloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{1a} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazolyl, methylpyrazolyl, piperidiny, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

[0103] In certain embodiments, R^{1a} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-

1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{1a} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, or phenoxy.

[0104] In certain embodiments, R^{1b} is H, deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0105] In certain embodiments, R^{1b} is H. In certain embodiments, R^{1b} is deuterium. In certain embodiments, R^{1b} is cyano. In certain embodiments, R^{1b} is halo. In certain embodiments, R^{1b} is fluoro or chloro. In certain embodiments, R^{1b} is fluoro. In certain embodiments, R^{1b} is chloro. In certain embodiments, R^{1b} is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1b} is methyl, ethyl, propyl, or butyl, each optionally substituted. In certain embodiments, R^{1b} is methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, or dimethylaminomethyl. In certain embodiments, R^{1b} is methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxy-methyl, or dimethylaminomethyl. In certain embodiments, R^{1b} is substituted or unsubstituted C₁-C₁₀ heteroalkyl.

[0106] In certain embodiments, R^{1b} is substituted or unsubstituted C₃-C₁₀ cycloalkyl. In certain embodiments, R^{1b} cyclobutyl or cyclohexyl, each optionally substituted. In certain embodiments, R^{1b} is substituted or unsubstituted C₆-C₁₄ aryl. In certain embodiments, R^{1b} is substituted or unsubstituted phenyl. In certain embodiments, R^{1b} is substituted or unsubstituted

C₇-C₁₅ arylalkyl. In certain embodiments, R^{1b} is substituted or unsubstituted heteroaryl. In certain embodiments, R^{1b} is substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{1b} is 5- or 6-membered heteroaryl, each optionally substituted. In certain embodiments, R^{1b} is substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{1b} is substituted or unsubstituted pyrazolyl. In certain embodiments, R^{1b} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted. In certain embodiments, R^{1b} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted with substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1b} is pyrazol-1-yl, 1-methylpyrazol-3-yl, 2-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{1b} is pyrazol-1-yl, 1-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{1b} is substituted or unsubstituted 6-membered heteroaryl.

[0107] In certain embodiments, R^{1b} is substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{1b} is substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{1b} is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted. In certain embodiments, R^{1b} is substituted or unsubstituted 3-membered heterocycloalkyl. In certain embodiments, R^{1b} is substituted or unsubstituted 4-membered heterocycloalkyl. In certain embodiments, R^{1b} is substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{1b} is substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{1b} is substituted or unsubstituted 7-membered heterocycloalkyl. In certain embodiments, R^{1b} is oxetanyl, oxanyl, piperidinyl, or morpholino, each optionally substituted. In certain embodiments, R^{1b} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, or morpholino, each optionally substituted. In certain embodiments, R^{1b} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, or morpholino. In certain embodiments, R^{1b} is piperidin-1-yl or morpholino.

[0108] In certain embodiments, R^{1b} is substituted or unsubstituted bicyclic heterocycloalkyl. In certain embodiments, R^{1b} is bridged, fused, or spiro heterocycloalkyl, each optionally substituted. In certain embodiments, R^{1b} is substituted or unsubstituted bridged heterocycloalkyl. In certain embodiments, R^{1b} is substituted or unsubstituted 8-azabicyclo[3.2.1]octanyl. In certain embodiments, R^{1b} is substituted or unsubstituted 8-azabicyclo[3.2.1]octan-8-yl. In certain embodiments, R^{1b} is substituted or unsubstituted fused heterocycloalkyl. In certain embodiments, R^{1b} is substituted or unsubstituted heterocycloalkyl.

[0109] In certain embodiments, R^{1b} is $-\text{COR}'$, wherein R' is as defined herein. In certain embodiments, R^{1b} is $-\text{COR}'$, wherein R' is substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{1b} is $-\text{CONR}'\text{R}''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{1b} is $-\text{CONR}'\text{R}''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{1b} is $-\text{OR}'$, wherein R' is as defined herein. In certain embodiments, R^{1b} is $-\text{OR}'$, wherein R' is independently H, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, or substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl. In certain embodiments, R^{1b} is $-\text{NR}'\text{R}''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{1b} is $-\text{NR}'\text{R}''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{1b} is $-\text{S(O)}_2\text{R}'$, wherein R' is as defined herein. In certain embodiments, R^{1b} is $-\text{S(O)}_2\text{R}'$, wherein R' is substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{1b} is $-\text{S(O)}_2\text{NR}'\text{R}''$; wherein R' and R'' are each as defined herein. In certain embodiments, R^{1b} is $-\text{S(O)}_2\text{NR}'\text{R}''$; wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl.

[0110] In certain embodiments, R^{1b} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidinyl, difluoropiperidinyl, (hydroxymethyl)piperidinyl, hydroxypiperidinyl, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidin-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{1b} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazolyl, methylpyrazolyl, piperidinyl, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

[0111] In certain embodiments, R^{1b} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino,

phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{1b} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo-[3.2.1]octan-8-yl, or phenoxy.

[0112] In certain embodiments, R^{1c} is H, deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0113] In certain embodiments, R^{1c} is H. In certain embodiments, R^{1c} is deuterium. In certain embodiments, R^{1c} is cyano. In certain embodiments, R^{1c} is halo. In certain embodiments, R^{1c} is fluoro or chloro. In certain embodiments, R^{1c} is fluoro. In certain embodiments, R^{1c} is chloro. In certain embodiments, R^{1c} is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1c} is methyl, ethyl, propyl, or butyl, each optionally substituted. In certain embodiments, R^{1c} is methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, or dimethylaminomethyl. In certain embodiments, R^{1c} is methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxy-methyl, or dimethylaminomethyl. In certain embodiments, R^{1c} is substituted or unsubstituted C₁-C₁₀ heteroalkyl.

[0114] In certain embodiments, R^{1c} is substituted or unsubstituted C₃-C₁₀ cycloalkyl. In certain embodiments, R^{1c} cyclobutyl or cyclohexyl, each optionally substituted. In certain embodiments, R^{1c} is substituted or unsubstituted C₆-C₁₄ aryl. In certain embodiments, R^{1c} is substituted or unsubstituted phenyl. In certain embodiments, R^{1c} is substituted or unsubstituted C₇-C₁₅ arylalkyl. In certain embodiments, R^{1c} is substituted or unsubstituted heteroaryl. In certain embodiments, R^{1c} is substituted or unsubstituted monocyclic heteroaryl. In certain

embodiments, R^{1c} is 5- or 6-membered heteroaryl, each optionally substituted. In certain embodiments, R^{1c} is substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{1c} is substituted or unsubstituted pyrazolyl. In certain embodiments, R^{1c} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted. In certain embodiments, R^{1c} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted with substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1c} is pyrazol-1-yl, 1-methylpyrazol-3-yl, 2-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{1c} is pyrazol-1-yl, 1-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{1c} is substituted or unsubstituted 6-membered heteroaryl.

[0115] In certain embodiments, R^{1c} is substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{1c} is substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{1c} is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted. In certain embodiments, R^{1c} is substituted or unsubstituted 3-membered heterocycloalkyl. In certain embodiments, R^{1c} is substituted or unsubstituted 4-membered heterocycloalkyl. In certain embodiments, R^{1c} is substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{1c} is substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{1c} is substituted or unsubstituted 7-membered heterocycloalkyl. In certain embodiments, R^{1c} is oxetanyl, oxanyl, piperidinyl, or morpholino, each optionally substituted. In certain embodiments, R^{1c} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, or morpholino, each optionally substituted. In certain embodiments, R^{1c} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, or morpholino. In certain embodiments, R^{1c} is piperidin-1-yl or morpholino.

[0116] In certain embodiments, R^{1c} is substituted or unsubstituted bicyclic heterocycloalkyl. In certain embodiments, R^{1c} is bridged, fused, or spiro heterocycloalkyl, each optionally substituted. In certain embodiments, R^{1c} is substituted or unsubstituted bridged heterocycloalkyl. In certain embodiments, R^{1c} is substituted or unsubstituted 8-azabicyclo[3.2.1]octanyl. In certain embodiments, R^{1c} is substituted or unsubstituted 8-azabicyclo[3.2.1]octan-8-yl. In certain embodiments, R^{1c} is substituted or unsubstituted fused heterocycloalkyl. In certain embodiments, R^{1c} is substituted or unsubstituted heterocycloalkyl.

[0117] In certain embodiments, R^{1c} is -COR', wherein R' is as defined herein. In certain embodiments, R^{1c} is -COR', wherein R' is substituted or unsubstituted C₁-C₁₀ alkyl. In certain

embodiments, R^{1c} is $-\text{CONR}'R''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{1c} is $-\text{CONR}'R''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{1c} is $-\text{OR}'$, wherein R' is as defined herein. In certain embodiments, R^{1c} is $-\text{OR}'$, wherein R' is independently H, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, or substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl. In certain embodiments, R^{1c} is $-\text{NR}'R''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{1c} is $-\text{NR}'R''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{1c} is $-\text{S(O)}_2R'$, wherein R' is as defined herein. In certain embodiments, R^{1c} is $-\text{S(O)}_2R'$, wherein R' is substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{1c} is $-\text{S(O)}_2\text{NR}'R''$; wherein R' and R'' are each as defined herein. In certain embodiments, R^{1c} is $-\text{S(O)}_2\text{NR}'R''$; wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl.

[0118] In certain embodiments, R^{1c} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidinyl, difluoropiperidinyl, (hydroxymethyl)piperidinyl, hydroxypiperidinyl, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyl, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{1c} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazolyl, methylpyrazolyl, piperidinyl, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

[0119] In certain embodiments, R^{1c} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{1c} is H, cyano, chloro, fluoro, methyl, trifluoromethyl,

ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo-[3.2.1]octan-8-yl, or phenoxy.

[0120] In certain embodiments, R^{1d} is H, deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R"; wherein each R' and R" is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0121] In certain embodiments, R^{1d} is H. In certain embodiments, R^{1d} is deuterium. In certain embodiments, R^{1d} is cyano. In certain embodiments, R^{1d} is halo. In certain embodiments, R^{1d} is fluoro or chloro. In certain embodiments, R^{1d} is fluoro. In certain embodiments, R^{1d} is chloro. In certain embodiments, R^{1d} is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1d} is methyl, ethyl, propyl, or butyl, each optionally substituted. In certain embodiments, R^{1d} is methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, or dimethylaminomethyl. In certain embodiments, R^{1d} is methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxy-methyl, or dimethylaminomethyl. In certain embodiments, R^{1d} is substituted or unsubstituted C₁-C₁₀ heteroalkyl.

[0122] In certain embodiments, R^{1d} is substituted or unsubstituted C₃-C₁₀ cycloalkyl. In certain embodiments, R^{1d} cyclobutyl or cyclohexyl, each optionally substituted. In certain embodiments, R^{1d} is substituted or unsubstituted C₆-C₁₄ aryl. In certain embodiments, R^{1d} is substituted or unsubstituted phenyl. In certain embodiments, R^{1d} is substituted or unsubstituted C₇-C₁₅ arylalkyl. In certain embodiments, R^{1d} is substituted or unsubstituted heteroaryl. In certain embodiments, R^{1d} is substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{1d} is 5- or 6-membered heteroaryl, each optionally substituted. In certain embodiments, R^{1d} is substituted or unsubstituted 5-membered heteroaryl. In certain

embodiments, R^{1d} is substituted or unsubstituted pyrazolyl. In certain embodiments, R^{1d} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted. In certain embodiments, R^{1d} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted with substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1d} is pyrazol-1-yl, 1-methylpyrazol-3-yl, 2-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{1d} is pyrazol-1-yl, 1-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{1d} is substituted or unsubstituted 6-membered heteroaryl.

[0123] In certain embodiments, R^{1d} is substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{1d} is substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{1d} is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted. In certain embodiments, R^{1d} is substituted or unsubstituted 3-membered heterocycloalkyl. In certain embodiments, R^{1d} is substituted or unsubstituted 4-membered heterocycloalkyl. In certain embodiments, R^{1d} is substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{1d} is substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{1d} is substituted or unsubstituted 7-membered heterocycloalkyl. In certain embodiments, R^{1d} is oxetanyl, oxanyl, piperidinyl, or morpholino, each optionally substituted. In certain embodiments, R^{1d} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, or morpholino, each optionally substituted. In certain embodiments, R^{1d} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, or morpholino. In certain embodiments, R^{1d} is piperidin-1-yl or morpholino.

[0124] In certain embodiments, R^{1d} is substituted or unsubstituted bicyclic heterocycloalkyl. In certain embodiments, R^{1d} is bridged, fused, or spiro heterocycloalkyl, each optionally substituted. In certain embodiments, R^{1d} is substituted or unsubstituted bridged heterocycloalkyl. In certain embodiments, R^{1d} is substituted or unsubstituted 8-azabicyclo[3.2.1]octanyl. In certain embodiments, R^{1d} is substituted or unsubstituted 8-azabicyclo[3.2.1]octan-8-yl. In certain embodiments, R^{1d} is substituted or unsubstituted fused heterocycloalkyl. In certain embodiments, R^{1d} is substituted or unsubstituted heterocycloalkyl.

[0125] In certain embodiments, R^{1d} is -COR', wherein R' is as defined herein. In certain embodiments, R^{1d} is -COR', wherein R' is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1d} is -CONR'R'', wherein R' and R'' are each as defined herein. In certain embodiments, R^{1d} is -CONR'R'', wherein R' and R'' are each independently H, or substituted or

unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1d} is -OR', wherein R' is as defined herein. In certain embodiments, R^{1d} is -OR', wherein R' is independently H, substituted or unsubstituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₆-C₁₄ aryl. In certain embodiments, R^{1d} is -NR'R'', wherein R' and R'' are each as defined herein. In certain embodiments, R^{1d} is -NR'R'', wherein R' and R'' are each independently H, or substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1d} is -S(O)₂R', wherein R' is as defined herein. In certain embodiments, R^{1d} is -S(O)₂R', wherein R' is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1d} is -S(O)₂NR'R'', wherein R' and R'' are each as defined herein. In certain embodiments, R^{1d} is -S(O)₂NR'R'', wherein R' and R'' are each independently H, or substituted or unsubstituted C₁-C₁₀ alkyl.

[0126] In certain embodiments, R^{1d} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidiny, difluoropiperidiny, (hydroxymethyl)piperidiny, hydroxypiperidiny, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{1d} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazolyl, methylpyrazolyl, piperidiny, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

[0127] In certain embodiments, R^{1d} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{1d} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-

1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo-[3.2.1]octan-8-yl, or phenoxy.

[0128] In certain embodiments, R^{1e} is H, deuterium, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-COR'$, $-CONR'R''$, $-OR'$, $-NR'R''$, $-S(O)_2R'$, or $-S(O)_2NR'R''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_1 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0129] In certain embodiments, R^{1e} is H. In certain embodiments, R^{1e} is deuterium. In certain embodiments, R^{1e} is cyano. In certain embodiments, R^{1e} is halo. In certain embodiments, R^{1e} is fluoro or chloro. In certain embodiments, R^{1e} is fluoro. In certain embodiments, R^{1e} is chloro. In certain embodiments, R^{1e} is substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{1e} is methyl, ethyl, propyl, or butyl, each optionally substituted. In certain embodiments, R^{1e} is methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, or dimethylaminomethyl. In certain embodiments, R^{1e} is methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxy-methyl, or dimethylaminomethyl. In certain embodiments, R^{1e} is substituted or unsubstituted C_1 - C_{10} heteroalkyl.

[0130] In certain embodiments, R^{1e} is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In certain embodiments, R^{1e} cyclobutyl or cyclohexyl, each optionally substituted. In certain embodiments, R^{1e} is substituted or unsubstituted C_6 - C_{14} aryl. In certain embodiments, R^{1e} is substituted or unsubstituted phenyl. In certain embodiments, R^{1e} is substituted or unsubstituted C_7 - C_{15} arylalkyl. In certain embodiments, R^{1e} is substituted or unsubstituted heteroaryl. In certain embodiments, R^{1e} is substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{1e} is 5- or 6-membered heteroaryl, each optionally substituted. In certain embodiments, R^{1e} is substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{1e} is substituted or unsubstituted pyrazolyl. In certain embodiments, R^{1e} is

pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted. In certain embodiments, R^{1e} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted with substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1e} is pyrazol-1-yl, 1-methylpyrazol-3-yl, 2-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{1e} is pyrazol-1-yl, 1-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{1e} is substituted or unsubstituted 6-membered heteroaryl.

[0131] In certain embodiments, R^{1e} is substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{1e} is substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{1e} is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted. In certain embodiments, R^{1e} is substituted or unsubstituted 3-membered heterocycloalkyl. In certain embodiments, R^{1e} is substituted or unsubstituted 4-membered heterocycloalkyl. In certain embodiments, R^{1e} is substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{1e} is substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{1e} is substituted or unsubstituted 7-membered heterocycloalkyl. In certain embodiments, R^{1e} is oxetanyl, oxanyl, piperidinyl, or morpholino, each optionally substituted. In certain embodiments, R^{1e} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, or morpholino, each optionally substituted. In certain embodiments, R^{1e} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, or morpholino. In certain embodiments, R^{1e} is piperidin-1-yl or morpholino.

[0132] In certain embodiments, R^{1e} is substituted or unsubstituted bicyclic heterocycloalkyl. In certain embodiments, R^{1e} is bridged, fused, or spiro heterocycloalkyl, each optionally substituted. In certain embodiments, R^{1e} is substituted or unsubstituted bridged heterocycloalkyl. In certain embodiments, R^{1e} is substituted or unsubstituted 8-azabicyclo[3.2.1]octanyl. In certain embodiments, R^{1e} is substituted or unsubstituted 8-azabicyclo[3.2.1]octan-8-yl. In certain embodiments, R^{1e} is substituted or unsubstituted fused heterocycloalkyl. In certain embodiments, R^{1e} is substituted or unsubstituted heterocycloalkyl.

[0133] In certain embodiments, R^{1e} is -COR', wherein R' is as defined herein. In certain embodiments, R^{1e} is -COR', wherein R' is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1e} is -CONR'R'', wherein R' and R'' are each as defined herein. In certain embodiments, R^{1e} is -CONR'R'', wherein R' and R'' are each independently H, or substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1e} is -OR', wherein R' is as defined herein.

In certain embodiments, R^{1e} is $-OR'$, wherein R' is independently H, substituted or unsubstituted C_1 - C_{10} alkyl, or substituted or unsubstituted C_6 - C_{14} aryl. In certain embodiments, R^{1e} is $-NR'R''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{1e} is $-NR'R''$, wherein R' and R'' are each independently H, or substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{1e} is $-S(O)_2R'$, wherein R' is as defined herein. In certain embodiments, R^{1e} is $-S(O)_2R'$, wherein R' is substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{1e} is $-S(O)_2NR'R''$; wherein R' and R'' are each as defined herein. In certain embodiments, R^{1e} is $-S(O)_2NR'R''$; wherein R' and R'' are each independently H, or substituted or unsubstituted C_1 - C_{10} alkyl.

[0134] In certain embodiments, R^{1e} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidiny, difluoropiperidiny, (hydroxymethyl)piperidiny, hydroxypiperidiny, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{1e} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazolyl, methylpyrazolyl, piperidiny, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

[0135] In certain embodiments, R^{1e} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{1e} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, or phenoxy.

[0136] In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form heteroaryl, optionally substituted with one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R'', wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0137] In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted 5- or 6-membered heteroaryl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted 6-membered heteroaryl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form furandiyl, imidazoldiyl, pyrroldiyl, pyrazoldiyl, 1,2,3-triazoldiyl, or pyridindiyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, halo, or substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form furan-2,3-diyl, imidazol-4,5-diyl, pyrrol-2,3-diyl, pyrazol-4,5-diyl, 1,2,3-triazol-4,5-diyl, or pyridin-2,3-diyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, fluoro, or methyl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form furan-2,3-diyl, 1-methylimidazol-4,5-diyl, pyrrol-2,3-diyl, 1-methylpyrrol-2,3-diyl, pyrazol-4,5-diyl, 1-methyl-pyrazol-4,5-diyl, 1-methyl-1,2,3-triazol-4,5-diyl, or pyridin-2,3-diyl.

[0138] In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form heterocycloalkyl, optionally substituted with one, two, or three substituents, each of which is independently deuterium, oxo, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R'', wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0139] In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted 5- or 6-membered heterocycloalkyl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form tetrahydrofurandiyl, pyrrolidindiyl, 1,3-dioxolandiyl, oxandiyl, or morpholindiyl, each optionally substituted with one or two substituents, each of which is independently oxo, cyano, halo, or substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form tetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyrrolidin-3,4-diyl, 1,3-dioxolan-4,5-diyl, oxan-2,3-diyl, or morpholin-2,3-diyl, each optionally substituted with one or two substituents, each of which is independently oxo, fluoro, or methyl. In certain embodiments, R^{1a} and R^{1b} together with the carbon atoms to which they are attached form tetrahydrofuran-2,3-diyl, 5,5-dimethyltetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyrrolidin-3,4-diyl, 2-oxopyrrolidin-3,4-diyl, 2,2-difluoro-1,3-dioxolan-4,5-diyl, 2,2-dimethyl-1,3-dioxolan-4,5-diyl, oxan-2,3-diyl, 4-methylmorpholin-2,3-diyl, or 5-oxomorpholin-2,3-diyl.

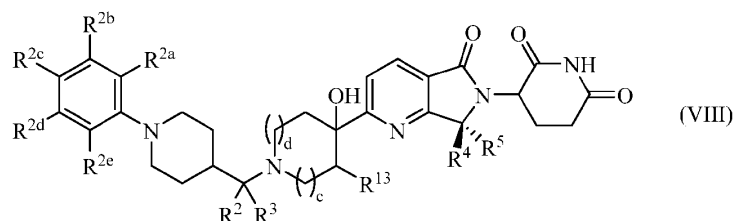
[0140] In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form heteroaryl, optionally substituted with one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_1 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0141] In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted 5- or 6-membered heteroaryl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted 6-membered heteroaryl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form furandiyl, imidazoldiyl, pyrroldiyl, pyrazoldiyl, 1,2,3-triazoldiyl, or pyridindiyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, halo, or substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form furan-2,3-diyl, imidazol-4,5-diyl, pyrrol-2,3-diyl, pyrazol-4,5-diyl, 1,2,3-triazol-4,5-diyl, or pyridin-2,3-diyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, fluoro, or methyl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form furan-2,3-diyl, 1-methylimidazol-4,5-diyl, pyrrol-2,3-diyl, 1-methylpyrrol-2,3-diyl, pyrazol-4,5-diyl, 1-methyl-pyrazol-4,5-diyl, 1-methyl-1,2,3-triazol-4,5-diyl, or pyridin-2,3-diyl.

[0142] In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form heterocycloalkyl, optionally substituted with one, two, or three substituents, each of which is independently deuterium, oxo, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R'', wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0143] In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted 5- or 6-membered heterocycloalkyl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form tetrahydrofurandiyl, pyrrolidindiyl, 1,3-dioxolandiyl, oxandiyl, or morpholindiyl, each optionally substituted with one or two substituents, each of which is independently oxo, cyano, halo, or substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form tetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyrrolidin-3,4-diyl, 1,3-dioxolan-4,5-diyl, oxan-2,3-diyl, or morpholin-2,3-diyl, each optionally substituted with one or two substituents, each of which is independently oxo, fluoro, or methyl. In certain embodiments, R^{1b} and R^{1c} together with the carbon atoms to which they are attached form tetrahydrofuran-2,3-diyl, 5,5-dimethyltetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyrrolidin-3,4-diyl, 2-oxopyrrolidin-3,4-diyl, 2,2-difluoro-1,3-dioxolan-4,5-diyl, 2,2-dimethyl-1,3-dioxolan-4,5-diyl, oxan-2,3-diyl, 4-methylmorpholin-2,3-diyl, or 5-oxomorpholin-2,3-diyl.

[0144] In yet another embodiment, provided herein is a compound having the structure of Formula (VIII):

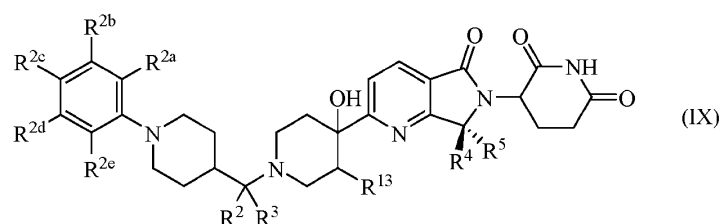


or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein:

R^{2a}, R^{2b}, R^{2c}, R^{2d}, and R^{2e} are each independently H, deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R'', wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl; or R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl; or R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl; and

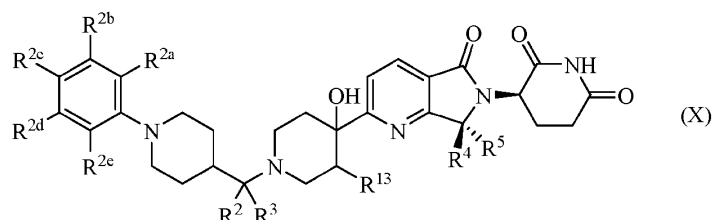
R², R³, R⁴, R⁵, R¹³, c, and d are each as defined herein.

[0145] In yet another embodiment, provided herein is a compound having the structure of Formula (IX):



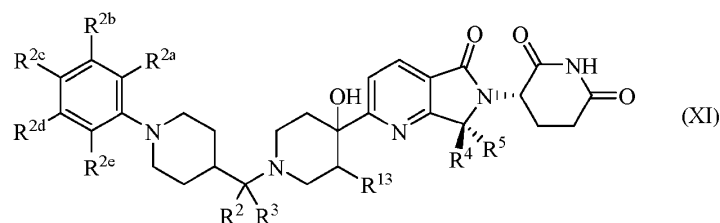
or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein R², R³, R⁴, R⁵, R¹³, R^{2a}, R^{2b}, R^{2c}, R^{2d}, and R^{2e} are each as defined herein.

[0146] In yet another embodiment, provided herein is a compound having the structure of Formula (X):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein R², R³, R⁴, R⁵, R¹³, R^{2a}, R^{2b}, R^{2c}, R^{2d}, and R^{2e} are each as defined herein.

[0147] In still another embodiment, provided herein is a compound having the structure of Formula (XI):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers thereof; or a pharmaceutically

acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein R^2 , R^3 , R^4 , R^5 , R^{13} , R^{2a} , R^{2b} , R^{2c} , R^{2d} , and R^{2e} are each as defined herein.

[0148] In certain embodiments, R^{2a} , R^{2b} , R^{2c} , R^{2d} , and R^{2e} are each independently H, deuterium, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_1 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0149] In certain embodiments, R^{2a} is H, deuterium, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_1 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0150] In certain embodiments, R^{2a} is H. In certain embodiments, R^{2a} is deuterium. In certain embodiments, R^{2a} is cyano. In certain embodiments, R^{2a} is halo. In certain embodiments, R^{2a} is fluoro or chloro. In certain embodiments, R^{2a} is fluoro. In certain embodiments, R^{2a} is chloro. In certain embodiments, R^{2a} is substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2a} is methyl, ethyl, propyl, or butyl, each optionally substituted. In certain embodiments, R^{2a} is methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, or dimethylaminomethyl. In certain embodiments, R^{2a} is methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxy-methyl, or dimethylaminomethyl. In certain embodiments, R^{2a} is substituted or unsubstituted C_1 - C_{10} heteroalkyl.

[0151] In certain embodiments, R^{2a} is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In certain embodiments, R^{2a} is cyclobutyl or cyclohexyl, each optionally substituted. In certain embodiments, R^{2a} is substituted or unsubstituted C_6 - C_{14} aryl. In certain embodiments, R^{2a} is substituted or unsubstituted phenyl. In certain embodiments, R^{2a} is substituted or unsubstituted C_7 - C_{15} arylalkyl. In certain embodiments, R^{2a} is substituted or unsubstituted heteroaryl. In certain embodiments, R^{2a} is substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{2a} is 5- or 6-membered heteroaryl, each optionally substituted. In certain embodiments, R^{2a} is substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{2a} is substituted or unsubstituted pyrazolyl. In certain embodiments, R^{2a} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted. In certain embodiments, R^{2a} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted with substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2a} is pyrazol-1-yl, 1-methylpyrazol-3-yl, 2-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{2a} is pyrazol-1-yl, 1-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{2a} is substituted or unsubstituted 6-membered heteroaryl.

[0152] In certain embodiments, R^{2a} is substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{2a} is substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{2a} is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted. In certain embodiments, R^{2a} is substituted or unsubstituted 3-membered heterocycloalkyl. In certain embodiments, R^{2a} is substituted or unsubstituted 4-membered heterocycloalkyl. In certain embodiments, R^{2a} is substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{2a} is substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{2a} is substituted or unsubstituted 7-membered heterocycloalkyl. In certain embodiments, R^{2a} is oxetanyl, oxanyl, piperidiny, or morpholino, each optionally substituted. In certain embodiments, R^{2a} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, or morpholino, each optionally substituted. In certain embodiments, R^{2a} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, or morpholino. In certain embodiments, R^{2a} is piperidin-1-yl or morpholino.

[0153] In certain embodiments, R^{2a} is substituted or unsubstituted bicyclic heterocycloalkyl. In certain embodiments, R^{2a} is bridged, fused, or spiro heterocycloalkyl, each optionally substituted. In certain embodiments, R^{2a} is substituted or unsubstituted bridged heterocycloalkyl.

In certain embodiments, R^{2a} is substituted or unsubstituted 8-azabicyclo[3.2.1]octanyl. In certain embodiments, R^{2a} is substituted or unsubstituted 8-azabicyclo[3.2.1]octan-8-yl. In certain embodiments, R^{2a} is substituted or unsubstituted fused heterocycloalkyl. In certain embodiments, R^{2a} is substituted or unsubstituted heterocycloalkyl.

[0154] In certain embodiments, R^{2a} is $-\text{COR}'$, wherein R' is as defined herein. In certain embodiments, R^{2a} is $-\text{COR}'$, wherein R' is substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2a} is $-\text{CONR}'\text{R}''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{2a} is $-\text{CONR}'\text{R}''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2a} is $-\text{OR}'$, wherein R' is as defined herein. In certain embodiments, R^{2a} is $-\text{OR}'$, wherein R' is independently H, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, or substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl. In certain embodiments, R^{2a} is $-\text{NR}'\text{R}''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{2a} is $-\text{NR}'\text{R}''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2a} is $-\text{S}(\text{O})_2\text{R}'$, wherein R' is as defined herein. In certain embodiments, R^{2a} is $-\text{S}(\text{O})_2\text{R}'$, wherein R' is substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2a} is $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein R' and R'' are each as defined herein. In certain embodiments, R^{2a} is $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl.

[0155] In certain embodiments, R^{2a} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methyl-pyrazolyl, oxetanyl, piperidiny, difluoropiperidiny, (hydroxymethyl)piperidiny, hydroxypiperidiny, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{2a} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazolyl, methyl-pyrazolyl, piperidiny, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

[0156] In certain embodiments, R^{2a} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-

1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{2a} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, or phenoxy.

[0157] In certain embodiments, R^{2b} is H, deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0158] In certain embodiments, R^{2b} is H. In certain embodiments, R^{2b} is deuterium. In certain embodiments, R^{2b} is cyano. In certain embodiments, R^{2b} is halo. In certain embodiments, R^{2b} is fluoro or chloro. In certain embodiments, R^{2b} is fluoro. In certain embodiments, R^{2b} is chloro. In certain embodiments, R^{2b} is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{2b} is methyl, ethyl, propyl, or butyl, each optionally substituted. In certain embodiments, R^{2b} is methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, or dimethylaminomethyl. In certain embodiments, R^{2b} is methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxy-methyl, or dimethylaminomethyl. In certain embodiments, R^{2b} is substituted or unsubstituted C₁-C₁₀ heteroalkyl.

[0159] In certain embodiments, R^{2b} is substituted or unsubstituted C₃-C₁₀ cycloalkyl. In certain embodiments, R^{2b} cyclobutyl or cyclohexyl, each optionally substituted. In certain

embodiments, R^{2b} is substituted or unsubstituted C₆-C₁₄ aryl. In certain embodiments, R^{2b} is substituted or unsubstituted phenyl. In certain embodiments, R^{2b} is substituted or unsubstituted C₇-C₁₅ arylalkyl. In certain embodiments, R^{2b} is substituted or unsubstituted heteroaryl. In certain embodiments, R^{2b} is substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{2b} is 5- or 6-membered heteroaryl, each optionally substituted. In certain embodiments, R^{2b} is substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{2b} is substituted or unsubstituted pyrazolyl. In certain embodiments, R^{2b} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted. In certain embodiments, R^{2b} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted with substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{2b} is pyrazol-1-yl, 1-methylpyrazol-3-yl, 2-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{2b} is pyrazol-1-yl, 1-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{2b} is substituted or unsubstituted 6-membered heteroaryl.

[0160] In certain embodiments, R^{2b} is substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{2b} is substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{2b} is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted. In certain embodiments, R^{2b} is substituted or unsubstituted 3-membered heterocycloalkyl. In certain embodiments, R^{2b} is substituted or unsubstituted 4-membered heterocycloalkyl. In certain embodiments, R^{2b} is substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{2b} is substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{2b} is substituted or unsubstituted 7-membered heterocycloalkyl. In certain embodiments, R^{2b} is oxetanyl, oxanyl, piperidiny, or morpholino, each optionally substituted. In certain embodiments, R^{2b} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, or morpholino, each optionally substituted. In certain embodiments, R^{2b} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, or morpholino. In certain embodiments, R^{2b} is piperidin-1-yl or morpholino.

[0161] In certain embodiments, R^{2b} is substituted or unsubstituted bicyclic heterocycloalkyl. In certain embodiments, R^{2b} is bridged, fused, or spiro heterocycloalkyl, each optionally substituted. In certain embodiments, R^{2b} is substituted or unsubstituted bridged heterocycloalkyl. In certain embodiments, R^{2b} is substituted or unsubstituted 8-azabicyclo[3.2.1]octanyl. In certain embodiments, R^{2b} is substituted or unsubstituted 8-azabicyclo[3.2.1]octan-8-yl. In certain

embodiments, R^{2b} is substituted or unsubstituted fused heterocycloalkyl. In certain embodiments, R^{2b} is substituted or unsubstituted heterocycloalkyl.

[0162] In certain embodiments, R^{2b} is $-\text{COR}'$, wherein R' is as defined herein. In certain embodiments, R^{2b} is $-\text{COR}'$, wherein R' is substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2b} is $-\text{CONR}'\text{R}''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{2b} is $-\text{CONR}'\text{R}''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2b} is $-\text{OR}'$, wherein R' is as defined herein. In certain embodiments, R^{2b} is $-\text{OR}'$, wherein R' is independently H, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, or substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl. In certain embodiments, R^{2b} is $-\text{NR}'\text{R}''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{2b} is $-\text{NR}'\text{R}''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2b} is $-\text{S}(\text{O})_2\text{R}'$, wherein R' is as defined herein. In certain embodiments, R^{2b} is $-\text{S}(\text{O})_2\text{R}'$, wherein R' is substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2b} is $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein R' and R'' are each as defined herein. In certain embodiments, R^{2b} is $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl.

[0163] In certain embodiments, R^{2b} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidiny, difluoropiperidiny, (hydroxymethyl)piperidiny, hydroxypiperidiny, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{2b} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazolyl, methylpyrazolyl, piperidiny, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

[0164] In certain embodiments, R^{2b} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-

1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{2b} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, or phenoxy.

[0165] In certain embodiments, R^{2c} is H, deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0166] In certain embodiments, R^{2c} is H. In certain embodiments, R^{2c} is deuterium. In certain embodiments, R^{2c} is cyano. In certain embodiments, R^{2c} is halo. In certain embodiments, R^{2c} is fluoro or chloro. In certain embodiments, R^{2c} is fluoro. In certain embodiments, R^{2c} is chloro. In certain embodiments, R^{2c} is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{2c} is methyl, ethyl, propyl, or butyl, each optionally substituted. In certain embodiments, R^{2c} is methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, or dimethylaminomethyl. In certain embodiments, R^{2c} is methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxy-methyl, or dimethylaminomethyl. In certain embodiments, R^{2c} is substituted or unsubstituted C₁-C₁₀ heteroalkyl.

[0167] In certain embodiments, R^{2c} is substituted or unsubstituted C₃-C₁₀ cycloalkyl. In certain embodiments, R^{2c} cyclobutyl or cyclohexyl, each optionally substituted. In certain embodiments, R^{2c} is substituted or unsubstituted C₆-C₁₄ aryl. In certain embodiments, R^{2c} is substituted or unsubstituted phenyl. In certain embodiments, R^{2c} is substituted or unsubstituted

C₇-C₁₅ arylalkyl. In certain embodiments, R^{2c} is substituted or unsubstituted heteroaryl. In certain embodiments, R^{2c} is substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{2c} is 5- or 6-membered heteroaryl, each optionally substituted. In certain embodiments, R^{2c} is substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{2c} is substituted or unsubstituted pyrazolyl. In certain embodiments, R^{2c} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted. In certain embodiments, R^{2c} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted with substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{2c} is pyrazol-1-yl, 1-methylpyrazol-3-yl, 2-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{2c} is pyrazol-1-yl, 1-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{2c} is substituted or unsubstituted 6-membered heteroaryl.

[0168] In certain embodiments, R^{2c} is substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{2c} is substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{2c} is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted. In certain embodiments, R^{2c} is substituted or unsubstituted 3-membered heterocycloalkyl. In certain embodiments, R^{2c} is substituted or unsubstituted 4-membered heterocycloalkyl. In certain embodiments, R^{2c} is substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{2c} is substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{2c} is substituted or unsubstituted 7-membered heterocycloalkyl. In certain embodiments, R^{2c} is oxetanyl, oxanyl, piperidinyl, or morpholino, each optionally substituted. In certain embodiments, R^{2c} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, or morpholino, each optionally substituted. In certain embodiments, R^{2c} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, or morpholino. In certain embodiments, R^{2c} is piperidin-1-yl or morpholino.

[0169] In certain embodiments, R^{2c} is substituted or unsubstituted bicyclic heterocycloalkyl. In certain embodiments, R^{2c} is bridged, fused, or spiro heterocycloalkyl, each optionally substituted. In certain embodiments, R^{2c} is substituted or unsubstituted bridged heterocycloalkyl. In certain embodiments, R^{2c} is substituted or unsubstituted 8-azabicyclo[3.2.1]octanyl. In certain embodiments, R^{2c} is substituted or unsubstituted 8-azabicyclo[3.2.1]octan-8-yl. In certain embodiments, R^{2c} is substituted or unsubstituted fused heterocycloalkyl. In certain embodiments, R^{2c} is substituted or unsubstituted heterocycloalkyl.

[0170] In certain embodiments, R^{2c} is $-\text{COR}'$, wherein R' is as defined herein. In certain embodiments, R^{2c} is $-\text{COR}'$, wherein R' is substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2c} is $-\text{CONR}'\text{R}''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{2c} is $-\text{CONR}'\text{R}''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2c} is $-\text{OR}'$, wherein R' is as defined herein. In certain embodiments, R^{2c} is $-\text{OR}'$, wherein R' is independently H, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, or substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl. In certain embodiments, R^{2c} is $-\text{NR}'\text{R}''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{2c} is $-\text{NR}'\text{R}''$, wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2c} is $-\text{S}(\text{O})_2\text{R}'$, wherein R' is as defined herein. In certain embodiments, R^{2c} is $-\text{S}(\text{O})_2\text{R}'$, wherein R' is substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl. In certain embodiments, R^{2c} is $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein R' and R'' are each as defined herein. In certain embodiments, R^{2c} is $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein R' and R'' are each independently H, or substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl.

[0171] In certain embodiments, R^{2c} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidiny, difluoropiperidiny, (hydroxymethyl)piperidiny, hydroxypiperidiny, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{2c} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazolyl, methylpyrazolyl, piperidiny, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

[0172] In certain embodiments, R^{2c} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino,

phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{2c} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo-[3.2.1]octan-8-yl, or phenoxy.

[0173] In certain embodiments, R^{2d} is H, deuterium, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-COR'$, $-CONR'R''$, $-OR'$, $-NR'R''$, $-S(O)_2R'$, or $-S(O)_2NR'R''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_1 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0174] In certain embodiments, R^{2d} is H. In certain embodiments, R^{2d} is deuterium. In certain embodiments, R^{2d} is cyano. In certain embodiments, R^{2d} is halo. In certain embodiments, R^{2d} is fluoro or chloro. In certain embodiments, R^{2d} is fluoro. In certain embodiments, R^{2d} is chloro. In certain embodiments, R^{2d} is substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2d} is methyl, ethyl, propyl, or butyl, each optionally substituted. In certain embodiments, R^{2d} is methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, or dimethylaminomethyl. In certain embodiments, R^{2d} is methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxy-methyl, or dimethylaminomethyl. In certain embodiments, R^{2d} is substituted or unsubstituted C_1 - C_{10} heteroalkyl.

[0175] In certain embodiments, R^{2d} is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In certain embodiments, R^{2d} cyclobutyl or cyclohexyl, each optionally substituted. In certain embodiments, R^{2d} is substituted or unsubstituted C_6 - C_{14} aryl. In certain embodiments, R^{2d} is substituted or unsubstituted phenyl. In certain embodiments, R^{2d} is substituted or unsubstituted C_7 - C_{15} arylalkyl. In certain embodiments, R^{2d} is substituted or unsubstituted heteroaryl. In certain embodiments, R^{2d} is substituted or unsubstituted monocyclic heteroaryl. In certain

embodiments, R^{2d} is 5- or 6-membered heteroaryl, each optionally substituted. In certain embodiments, R^{2d} is substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{2d} is substituted or unsubstituted pyrazolyl. In certain embodiments, R^{2d} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted. In certain embodiments, R^{2d} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted with substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2d} is pyrazol-1-yl, 1-methylpyrazol-3-yl, 2-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{2d} is pyrazol-1-yl, 1-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{2d} is substituted or unsubstituted 6-membered heteroaryl.

[0176] In certain embodiments, R^{2d} is substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{2d} is substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{2d} is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted. In certain embodiments, R^{2d} is substituted or unsubstituted 3-membered heterocycloalkyl. In certain embodiments, R^{2d} is substituted or unsubstituted 4-membered heterocycloalkyl. In certain embodiments, R^{2d} is substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{2d} is substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{2d} is substituted or unsubstituted 7-membered heterocycloalkyl. In certain embodiments, R^{2d} is oxetanyl, oxanyl, piperidinyl, or morpholino, each optionally substituted. In certain embodiments, R^{2d} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, or morpholino, each optionally substituted. In certain embodiments, R^{2d} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, or morpholino. In certain embodiments, R^{2d} is piperidin-1-yl or morpholino.

[0177] In certain embodiments, R^{2d} is substituted or unsubstituted bicyclic heterocycloalkyl. In certain embodiments, R^{2d} is bridged, fused, or spiro heterocycloalkyl, each optionally substituted. In certain embodiments, R^{2d} is substituted or unsubstituted bridged heterocycloalkyl. In certain embodiments, R^{2d} is substituted or unsubstituted 8-azabicyclo[3.2.1]octanyl. In certain embodiments, R^{2d} is substituted or unsubstituted 8-azabicyclo[3.2.1]octan-8-yl. In certain embodiments, R^{2d} is substituted or unsubstituted fused heterocycloalkyl. In certain embodiments, R^{2d} is substituted or unsubstituted heterocycloalkyl.

[0178] In certain embodiments, R^{2d} is $-\text{COR}'$, wherein R' is as defined herein. In certain embodiments, R^{2d} is $-\text{COR}'$, wherein R' is substituted or unsubstituted C_1 - C_{10} alkyl. In certain

embodiments, R^{2d} is $-\text{CONR}'R''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{2d} is $-\text{CONR}'R''$, wherein R' and R'' are each independently H, or substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2d} is $-\text{OR}'$, wherein R' is as defined herein. In certain embodiments, R^{2d} is $-\text{OR}'$, wherein R' is independently H, substituted or unsubstituted C_1 - C_{10} alkyl, or substituted or unsubstituted C_6 - C_{14} aryl. In certain embodiments, R^{2d} is $-\text{NR}'R''$, wherein R' and R'' are each as defined herein. In certain embodiments, R^{2d} is $-\text{NR}'R''$, wherein R' and R'' are each independently H, or substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2d} is $-\text{S(O)}_2R'$, wherein R' is as defined herein. In certain embodiments, R^{2d} is $-\text{S(O)}_2R'$, wherein R' is substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2d} is $-\text{S(O)}_2\text{NR}'R''$; wherein R' and R'' are each as defined herein. In certain embodiments, R^{2d} is $-\text{S(O)}_2\text{NR}'R''$; wherein R' and R'' are each independently H, or substituted or unsubstituted C_1 - C_{10} alkyl.

[0179] In certain embodiments, R^{2d} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methyl-pyrazolyl, oxetanyl, piperidinyl, difluoropiperidinyl, (hydroxymethyl)piperidinyl, hydroxypiperidinyl, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidin-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{2d} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazolyl, methyl-pyrazolyl, piperidinyl, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

[0180] In certain embodiments, R^{2d} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{2d} is H, cyano, chloro, fluoro, methyl, trifluoromethyl,

ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo-[3.2.1]octan-8-yl, or phenoxy.

[0181] In certain embodiments, R^{2e} is H, deuterium, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-COR'$, $-CONR'R''$, $-OR'$, $-NR'R''$, $-S(O)_2R'$, or $-S(O)_2NR'R''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_1 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0182] In certain embodiments, R^{2e} is H. In certain embodiments, R^{2e} is deuterium. In certain embodiments, R^{2e} is cyano. In certain embodiments, R^{2e} is halo. In certain embodiments, R^{2e} is fluoro or chloro. In certain embodiments, R^{2e} is fluoro. In certain embodiments, R^{2e} is chloro. In certain embodiments, R^{2e} is substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2e} is methyl, ethyl, propyl, or butyl, each optionally substituted. In certain embodiments, R^{2e} is methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, or dimethylaminomethyl. In certain embodiments, R^{2e} is methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxy-methyl, or dimethylaminomethyl. In certain embodiments, R^{2e} is substituted or unsubstituted C_1 - C_{10} heteroalkyl.

[0183] In certain embodiments, R^{2e} is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In certain embodiments, R^{2e} cyclobutyl or cyclohexyl, each optionally substituted. In certain embodiments, R^{2e} is substituted or unsubstituted C_6 - C_{14} aryl. In certain embodiments, R^{2e} is substituted or unsubstituted phenyl. In certain embodiments, R^{2e} is substituted or unsubstituted C_7 - C_{15} arylalkyl. In certain embodiments, R^{2e} is substituted or unsubstituted heteroaryl. In certain embodiments, R^{2e} is substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{2e} is 5- or 6-membered heteroaryl, each optionally substituted. In certain embodiments, R^{2e} is substituted or unsubstituted 5-membered heteroaryl. In certain

embodiments, R^{2e} is substituted or unsubstituted pyrazolyl. In certain embodiments, R^{2e} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted. In certain embodiments, R^{2e} is pyrazol-1-yl, pyrazol-3-yl, or pyrazol-4-yl, each optionally substituted with substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{2e} is pyrazol-1-yl, 1-methylpyrazol-3-yl, 2-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{2e} is pyrazol-1-yl, 1-methylpyrazol-3-yl, or 1-methylpyrazol-4-yl. In certain embodiments, R^{2e} is substituted or unsubstituted 6-membered heteroaryl.

[0184] In certain embodiments, R^{2e} is substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{2e} is substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{2e} is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted. In certain embodiments, R^{2e} is substituted or unsubstituted 3-membered heterocycloalkyl. In certain embodiments, R^{2e} is substituted or unsubstituted 4-membered heterocycloalkyl. In certain embodiments, R^{2e} is substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{2e} is substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{2e} is substituted or unsubstituted 7-membered heterocycloalkyl. In certain embodiments, R^{2e} is oxetanyl, oxanyl, piperidinyl, or morpholino, each optionally substituted. In certain embodiments, R^{2e} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, or morpholino, each optionally substituted. In certain embodiments, R^{2e} is oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, or morpholino. In certain embodiments, R^{2e} is piperidin-1-yl or morpholino.

[0185] In certain embodiments, R^{2e} is substituted or unsubstituted bicyclic heterocycloalkyl. In certain embodiments, R^{2e} is bridged, fused, or spiro heterocycloalkyl, each optionally substituted. In certain embodiments, R^{2e} is substituted or unsubstituted bridged heterocycloalkyl. In certain embodiments, R^{2e} is substituted or unsubstituted 8-azabicyclo[3.2.1]octanyl. In certain embodiments, R^{2e} is substituted or unsubstituted 8-azabicyclo[3.2.1]octan-8-yl. In certain embodiments, R^{2e} is substituted or unsubstituted fused heterocycloalkyl. In certain embodiments, R^{2e} is substituted or unsubstituted heterocycloalkyl.

[0186] In certain embodiments, R^{2e} is -COR', wherein R' is as defined herein. In certain embodiments, R^{2e} is -COR', wherein R' is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{2e} is -CONR'R'', wherein R' and R'' are each as defined herein. In certain embodiments, R^{2e} is -CONR'R'', wherein R' and R'' are each independently H, or substituted or

unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{2e} is -OR', wherein R' is as defined herein. In certain embodiments, R^{2e} is -OR', wherein R' is independently H, substituted or unsubstituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₆-C₁₄ aryl. In certain embodiments, R^{2e} is -NR'R'', wherein R' and R'' are each as defined herein. In certain embodiments, R^{2e} is -NR'R'', wherein R' and R'' are each independently H, or substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{2e} is -S(O)₂R', wherein R' is as defined herein. In certain embodiments, R^{2e} is -S(O)₂R', wherein R' is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R^{2e} is -S(O)₂NR'R'', wherein R' and R'' are each as defined herein. In certain embodiments, R^{2e} is -S(O)₂NR'R'', wherein R' and R'' are each independently H, or substituted or unsubstituted C₁-C₁₀ alkyl.

[0187] In certain embodiments, R^{2e} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methyl-pyrazolyl, oxetanyl, piperidiny, difluoropiperidiny, (hydroxymethyl)piperidiny, hydroxypiperidiny, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{2e} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazolyl, methyl-pyrazolyl, piperidiny, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

[0188] In certain embodiments, R^{2e} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl. In certain embodiments, R^{2e} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-

1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo-[3.2.1]octan-8-yl, or phenoxy.

[0189] In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form heteroaryl, optionally substituted with one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_1 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0190] In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted 5- or 6-membered heteroaryl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted 6-membered heteroaryl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form furandiyl, imidazoldiyl, pyrroldiyl, pyrazoldiyl, 1,2,3-triazoldiyl, or pyridindiyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, halo, or substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form furan-2,3-diyl, imidazol-4,5-diyl, pyrrol-2,3-diyl, pyrazol-4,5-diyl, 1,2,3-triazol-4,5-diyl, or pyridin-2,3-diyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, fluoro, or methyl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached

form furan-2,3-diyl, 1-methylimidazol-4,5-diyl, pyrrol-2,3-diyl, 1-methylpyrrol-2,3-diyl, pyrazol-4,5-diyl, 1-methyl-pyrazol-4,5-diyl, 1-methyl-1,2,3-triazol-4,5-diyl, or pyridin-2,3-diyl.

[0191] In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form heterocycloalkyl, optionally substituted with one, two, or three substituents, each of which is independently deuterium, oxo, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_1 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0192] In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted 5- or 6-membered heterocycloalkyl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form tetrahydrofurandiyl, pyrrolidindiyl, 1,3-dioxolandiyl, oxandiyl, or morpholindiyl, each optionally substituted with one or two substituents, each of which is independently oxo, cyano, halo, or substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form tetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyrrolidin-3,4-diyl, 1,3-dioxolan-4,5-diyl, oxan-2,3-diyl, or morpholin-2,3-diyl, each optionally substituted with one or two substituents, each of which is independently oxo, fluoro, or methyl. In certain embodiments, R^{2a} and R^{2b} together with the carbon atoms to which they are attached form tetrahydrofuran-2,3-diyl, 5,5-dimethyltetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyrrolidin-3,4-diyl, 2-oxopyrrolidin-

3,4-diyl, 2,2-difluoro-1,3-dioxolan-4,5-diyl, 2,2-dimethyl-1,3-dioxolan-4,5-diyl, oxan-2,3-diyl, 4-methylmorpholin-2,3-diyl, or 5-oxomorpholin-2,3-diyl.

[0193] In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form heteroaryl, optionally substituted with one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_1 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0194] In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted monocyclic heteroaryl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted 5- or 6-membered heteroaryl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted 5-membered heteroaryl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted 6-membered heteroaryl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form furandiyl, imidazoldiyl, pyrroldiyl, pyrazoldiyl, 1,2,3-triazoldiyl, or pyridindiyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, halo, or substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form furan-2,3-diyl, imidazol-4,5-diyl, pyrrol-2,3-diyl, pyrazol-4,5-diyl, 1,2,3-triazol-4,5-diyl, or pyridin-2,3-diyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, fluoro, or methyl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached

form furan-2,3-diyl, 1-methylimidazol-4,5-diyl, pyrrol-2,3-diyl, 1-methylpyrrol-2,3-diyl, pyrazol-4,5-diyl, 1-methyl-pyrazol-4,5-diyl, 1-methyl-1,2,3-triazol-4,5-diyl, or pyridin-2,3-diyl.

[0195] In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted heterocycloalkyl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form heterocycloalkyl, optionally substituted with one, two, or three substituents, each of which is independently deuterium, oxo, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_1 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0196] In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted monocyclic heterocycloalkyl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted 5- or 6-membered heterocycloalkyl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted 5-membered heterocycloalkyl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form substituted or unsubstituted 6-membered heterocycloalkyl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form tetrahydrofurandiyl, pyrrolidindiyl, 1,3-dioxolandiyl, oxandiyl, or morpholindiyl, each optionally substituted with one or two substituents, each of which is independently oxo, cyano, halo, or substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form tetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyrrolidin-3,4-diyl, 1,3-dioxolan-4,5-diyl, oxan-2,3-diyl, or morpholin-2,3-diyl, each optionally substituted with one or two substituents, each of which is independently oxo, fluoro, or methyl. In certain embodiments, R^{2b} and R^{2c} together with the carbon atoms to which they are attached form tetrahydrofuran-2,3-diyl, 5,5-dimethyltetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyrrolidin-3,4-diyl, 2-oxopyrrolidin-

3,4-diyl, 2,2-difluoro-1,3-dioxolan-4,5-diyl, 2,2-dimethyl-1,3-dioxolan-4,5-diyl, oxan-2,3-diyl, 4-methylmorpholin-2,3-diyl, or 5-oxomorpholin-2,3-diyl.

[0197] In certain embodiments, R^2 is H, substituted or unsubstituted C_1 - C_{10} alkyl, or substituted or unsubstituted C_3 - C_{10} cycloalkyl. In certain embodiments, R^2 is H, or substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^2 is H. In certain embodiments, R^2 is substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^2 is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In certain embodiments, R^2 is substituted or unsubstituted monocyclic C_3 - C_{10} cycloalkyl.

[0198] In certain embodiments, R^3 is H, substituted or unsubstituted C_1 - C_{10} alkyl, or substituted or unsubstituted C_3 - C_{10} cycloalkyl. In certain embodiments, R^3 is H, or substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^3 is H. In certain embodiments, R^3 is substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^3 is substituted or unsubstituted C_3 - C_{10} cycloalkyl. In certain embodiments, R^3 is substituted or unsubstituted monocyclic C_3 - C_{10} cycloalkyl.

[0199] In certain embodiments, R^2 and R^3 are each independently H, alkyl, or cycloalkyl. In certain embodiments, R^2 and R^3 are each independently H or alkyl. In certain embodiments, R^2 and R^3 are each independently H or methyl. In certain embodiments, R^2 is methyl and R^3 is H. In certain embodiments, R^2 and R^3 are each H. In certain embodiments, R^2 and R^3 together form spirocyclopropyl.

[0200] In certain embodiments, R^2 and R^3 together with the carbon atom to which they are attached form $C(O)$ or substituted or unsubstituted C_3 - C_{10} cycloalkyl. In certain embodiments, R^2 and R^3 together with the carbon atom to which they are attached form $C(O)$. In certain embodiments, R^2 and R^3 together with the carbon atom to which they are attached form substituted or unsubstituted C_3 - C_{10} cycloalkyl. In certain embodiments, R^2 and R^3 together with the carbon atom to which they are attached form substituted or unsubstituted monocyclic C_3 - C_{10} cycloalkyl.

[0201] In certain embodiments, R^4 is H, substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^4 is H. In certain embodiments, R^4 is substituted or unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^4 is unsubstituted C_1 - C_{10} alkyl. In certain embodiments, R^4 is methyl.

- [0202] In certain embodiments, R⁵ is H, substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R⁵ is H. In certain embodiments, R⁵ is substituted or unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R⁵ is unsubstituted C₁-C₁₀ alkyl. In certain embodiments, R⁵ is methyl.
- [0203] In certain embodiments, R⁴ and R⁵ are each independently H or alkyl. In certain embodiments, R⁴ and R⁵ are each independently H or methyl. In certain embodiments, R⁴ is H and R⁵ is methyl. In certain embodiments, R⁴ is methyl and R⁵ is H. In certain embodiments, R⁴ and R⁵ are each H.
- [0204] In certain embodiments, R⁶ is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In certain embodiments, R⁶ is heterocycloalkyl or aryl.
- [0205] In certain embodiments, R⁷ and R⁸ are each independently H, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In certain embodiments, R⁷ is H; and R⁸ is heterocycloalkyl or aryl.
- [0206] In certain embodiments, R⁹, R¹⁰, and R¹¹ are each independently monocyclic or bridged or spiro bicyclic cycloalkyl or monocyclic or bridged or spiro bicyclic heterocycloalkyl. In certain embodiments, R⁹, R¹⁰, and R¹¹ are each independently monocyclic or bridged or spiro bicyclic heterocycloalkyl.
- [0207] In certain embodiments, R¹² is alkyl, aryl or heteroaryl. In certain embodiments, R¹² is alkyl or aryl. In certain embodiments, R¹² is alkyl. In certain embodiments, R¹² is aryl.
- [0208] In certain embodiments, R¹³ is H. In certain embodiments, R¹³ is hydroxyl.
- [0209] In certain embodiments, a is an integer of 1. In certain embodiments, a is an integer of 2. In certain embodiments, a is an integer of 3.
- [0210] In certain embodiments, b is an integer of 1. In certain embodiments, b is an integer of 2. In certain embodiments, b is an integer of 3.
- [0211] In certain embodiments, c is an integer of 0. In certain embodiments, c is an integer of 1. In certain embodiments, c is an integer of 2.
- [0212] In certain embodiments, d is an integer of 0. In certain embodiments, d is an integer of 1. In certain embodiments, d is an integer of 2.
- [0213] In certain embodiments, m, n, and q are each independently an integer of 0 or 1. In certain embodiments, m is an integer of 0. In certain embodiments, n is an integer of 1. In certain embodiments, p is an integer of 2. In certain embodiments, q is an integer of 0.
- [0214] In certain embodiments, each alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl,

arylalkyl, heteroaryl, heterocycloalkyl, alkoxy, alkylamino, and alkylthio described herein is optionally substituted with one, two, three, or four substituents, each of which is independently deuterium, cyano, halo, oxo, nitro, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CO₂R', -CONR'R'', -OR', -OC(O)R', -OC(O)NR'R'', -NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NR'C(O)NR''R''', -NRSO₂R', -NRSO₂NR'R'', -SR', -S(O)R', -S(O)₂R', or -S(O)₂NR'R''; wherein R', R'', and R''' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0215] In certain embodiments, each alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heterocycloalkyl, alkoxy, and alkylamino is optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''; wherein each R' and R'' is independently hydrogen, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₁-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0216] The groups, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R', R'', R''', R''', X, a, b, c, d, m, n, p, q, s, and t, in formulae described herein, including Formulae (I) to (XI) and (Ia), are defined in the embodiments described herein. All combinations of the embodiments provided herein for such groups are within the scope of this disclosure.

[0217] In certain embodiments, the compound provided herein is neither *tert*-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidine-1-carboxylate nor 3-[2-[1-[4-[4-[6-[(6-acetyl-8-cyclopentyl-7,8-dihydro-5-methyl-7-oxopyrido-

[2,3-*d*]pyrimidin-2-yl)amino]-3-pyridinyl]-1-piperidinyl]phenyl]methyl]-4-hydroxy-4-piperidinyl]-5,7-dihydro-5-oxo-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-2,6-piperidinedione.

[0218] In certain embodiments, the compound provided herein is not 3-[2-[1-[[4-[4-[6-[(6-acetyl-8-cyclopentyl-7,8-dihydro-5-methyl-7-oxopyrido-[2,3-*d*]pyrimidin-2-yl)amino]-3-pyridinyl]-1-piperidinyl]phenyl]methyl]-4-hydroxy-4-piperidinyl]-5,7-dihydro-5-oxo-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-2,6-piperidinedione trifluoroacetate.

[0219] In certain embodiments, the compound for use in the compositions and methods provided herein is 3-(2-(1-benzyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A001**.

[0220] In certain embodiments, the compound for use in the compositions and methods provided herein is:

3-(2-(1-benzyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A001**;

3-(2-(4-hydroxy-1-(pyridin-4-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A002**;

3-(2-(4-hydroxy-1-(2-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A003**;

3-(2-(4-hydroxy-1-(4-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A004**;

3-(2-(4-hydroxy-1-phenethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A005**;

3-(2-(4-hydroxy-1-(2-hydroxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A006**;

3-(2-(4-hydroxy-1-(3-hydroxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A007**;

3-(2-(4-hydroxy-1-(2-cyanobenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A008**;

3-(2-(4-hydroxy-1-(4-cyanobenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A009**;

3-(2-(4-hydroxy-1-(3-cyanobenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A010**;

3-(2-(4-hydroxy-1-(4-(hydroxymethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A011**;

3-(2-(1-(4-chlorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A012**;

3-(2-(1-(2,4-difluorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A013**;

3-(2-(1-(4-(dimethylamino)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A014**;

3-(2-(1-([1,1'-biphenyl]-4-ylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A015**;

3-(2-(4-hydroxy-1-(4-(methylsulfonyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A016**;

3-(2-(4-hydroxy-1-(3-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A017**;

3-(2-(4-hydroxy-1-(3-phenoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A018**;

3-(2-(1-(cyclohexylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A019**;

3-(2-(4-hydroxy-1-(3-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A020**;

3-(2-(1-(3-aminobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A021**;

3-(2-(4-hydroxy-1-((2-oxo-1,2-dihydropyridin-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A022**;

3-(2-(4-hydroxy-1-(2-methoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A023**;

3-(2-(4-hydroxy-1-(3-methoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A024**;

3-(2-(4-hydroxy-1-(4-methoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A025**;

3-(2-(1-(3-chlorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A026**;

3-(2-(1-(benzofuran-6-ylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A027**;

3-(2-(1-((1*H*-indazol-5-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A028**;

3-(2-(4-hydroxy-1-(pyrazolo[1,5-*a*]pyridin-6-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A029**;

3-(2-(1-((2,3-dihydro-1*H*-inden-2-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A030**;

3-(2-(4-hydroxy-1-(4-aminocarbonylphenylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A031**;

3-(2-(4-hydroxy-1-(3-aminocarbonylphenylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A032**;

3-(2-(1-(3-(dimethylamino)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A033**;

3-(2-(4-hydroxy-1-(4-(methoxymethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A034**;

3-(2-(4-hydroxy-1-(quinolin-6-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A035**;

3-(2-(4-hydroxy-1-((1-methyl-1*H*-indazol-6-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A036**;

3-(2-(1-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A037**;

3-(2-(4-hydroxy-1-((1-phenyl-1*H*-pyrazol-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A038**;

3-(2-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A039**;

4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)-*N,N*-dimethylbenzamide **A040**;

3-(2-(1-((2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A041**;

3-(2-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A042**;

3-(2-(1-(4-(benzyloxy)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A043**;

3-(2-(4-hydroxy-1-((1-methyl-1*H*-indazol-5-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A044**;

3-(2-(4-hydroxy-1-((1-methyl-1*H*-pyrazol-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A045**;

4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)-*N*-methylbenzamide **A046**;

3-(2-(4-hydroxy-1-((1-(trifluoromethyl)-1*H*-pyrazol-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A047**;

3-(2-(4-hydroxy-1-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A048**;

3-(2-(4-hydroxy-1-((1-phenylpiperidin-4-yl)methyl)piperidin-4-yl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A049**;

3-(2-(4-hydroxy-1-(4-(phenylamino)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A050**;

3-(2-(4-hydroxy-1-(4-(4-hydroxypiperidin-1-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A051**;

3-(2-(1-((1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A052**;

3-(2-(1-((2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A053**;

3-(2-(1-((2,2-dimethyl-2,3-dihydrobenzofuran-6-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A054**;

3-(2-(4-hydroxy-1-(isoxazol-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A055**;

3-(2-(4-hydroxy-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A056**;

3-(2-(4-hydroxy-1-((1-methyl-1H-benzo[*d*][1,2,3]triazol-5-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A057**;

3-(2-(1-(4-((dimethylamino)methyl)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A058**;

3-(2-(4-hydroxy-1-(4-phenoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A059**;

3-(2-(4-hydroxy-1-(4-((tetrahydro-2H-pyran-4-yl)oxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A060**;

3-(2-(4-hydroxy-1-(4-(4-(hydroxymethyl)piperidin-1-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A061**;

3-(2-(4-hydroxy-1-(4-(phoxymethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A062**;

3-(2-(1-((1-(3-chlorophenyl)-4-piperidyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A063**;

3-(2-(1-((1-(2-chlorophenyl)-4-piperidyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A064**;

3-(2-(1-((1-(4-chlorophenyl)piperidin-4-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A065**;

3-(2-(4-hydroxy-1-((4-(1-methylpyrazol-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A066**;

3-(2-(4-hydroxy-1-((4-(2-methylpyrazol-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A067**;

3-(2-(4-hydroxy-1-((4-pyrazol-1-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A068**;

3-(2-(4-hydroxy-1-((1-(2-pyridyl)-4-piperidyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A069**;

3-(2-(4-hydroxy-1-(((*R*)-1-phenylpiperidin-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A070**;

3-(2-(4-hydroxy-1-((1-(pyridin-3-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A071**;

3-(2-(4-hydroxy-1-((8-phenyl-8-azabicyclo[3.2.1]octan-3-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A072**;

3-(2-(4-hydroxy-1-((1-phenylazetidin-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A073**;

3-(2-(1-(4-chlorobenzoyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A074**;

3-(2-(1-(3,4-dimethoxybenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A075**;

3-(2-(4-hydroxy-1-((1-methylindol-5-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A076**;

3-(2-(4-hydroxy-1-((1-methylindazol-4-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A077**;

3-(2-(4-hydroxy-1-((4-(oxetan-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A078**;

3-(2-(4-hydroxy-1-((3-(1-piperidyl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A079**;

3-(2-(1-((4-(4,4-difluoro-1-piperidyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A080**;

3-(2-(4-hydroxy-1-(4-(piperidin-1-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A081**;

3-(2-(4-hydroxy-1-((4-tetrahydropyran-4-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A082**;

3-(2-(4-hydroxy-1-(3-(tetrahydro-2*H*-pyran-4-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A083**;

3-(2-(1-((3-fluorophenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A084**;

3-(2-(4-hydroxy-1-((4-morpholinophenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A085**;

3-(2-(4-hydroxy-1-((3-morpholinophenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A086**;

3-(2-(4-hydroxy-1-((3-(oxetan-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo-[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A087**;

3-(2-(4-hydroxy-1-((4-(tetrahydropyran-4-ylmethyl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A088**;

3-(2-(1-((2-fluorophenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A089**;

3-(2-(4-hydroxy-1-isobutyl-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-piperidine-2,6-dione **A090**;

3-(2-(1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A091**;

3-(2-(4-hydroxy-1-((1-methylbenzimidazol-5-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A092**;

3-(2-(4-hydroxy-1-((3-methylbenzimidazol-5-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A093**;

3-(2-(4-hydroxy-1-((1-methylindol-6-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A094**;

3-(2-(4-hydroxy-1-((4-(morpholinomethyl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A095**;

3-(2-(1-((4-fluorophenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A096**;

(3*S*)-3-((7*S*)-2-(1-benzyl-4-hydroxy-4-piperidyl)-7-methyl-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A097**;

(*S*)-3-((*R*)-2-(4-hydroxy-1-((1-phenylpiperidin-4-yl)methyl)piperidin-4-yl)-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A098**;

3-(2-(1-(2-(3-fluorophenyl)ethyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A099**;

3-(2-(1-(chroman-7-ylmethyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A100**;

3-(2-(1-(chroman-6-ylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A101**;

3-(2-(1-((2,3-dihydrobenzofuran-6-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A102**;

3-(2-(1-(2,3-dihydrobenzofuran-5-ylmethyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A103**;

3-(2-(1-(1,3-dihydroisobenzofuran-5-ylmethyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A104**;

3-(2-((3*S*,4*S*)-1-benzyl-3,4-dihydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A105**;

3-(2-((3*R*,4*R*)-1-benzyl-3,4-dihydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A106**;

3-(2-(1-((3,4-bis(trifluoromethyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A107**;

3-(2-(1-((4-*tert*-butylphenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A108**;

3-(2-(1-((3-*tert*-butylphenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A109**;

3-(2-(4-hydroxy-1-((4-isopropylphenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A110**;

3-(2-(4-hydroxy-1-((3-isopropylphenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A111**;

3-(2-(1-((3-(1,1-difluoroethyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A112**;

3-(2-(1-((4-(1,1-difluoroethyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A113**;

3-(2-(1-(4-ethylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A114**;

3-(2-(1-(4-chloro-3-methylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A115**;

3-(2-(1-(4-((1*R*,5*S*)-8-azabicyclo[3.2.1]octan-8-yl)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A116**;

3-(2-(1-(4-cyclobutylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A117**;

3-(2-(1-(3-ethylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A118**;

3-(2-(1-(4-chloro-3-fluorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A119**;

3-(2-(1-(3-cyclobutylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A120**;

3-(2-(1-((1*R*,5*S*)-8-azabicyclo[3.2.1]octan-8-yl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A121**;

3-(2-(1-(4-cyclohexylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A122**;

4-((4-(6-((*S*)-2,6-dioxopiperidin-3-yl)-7-methyl-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile **A123**;

4-((4-((*R*)-6-((*S*)-2,6-dioxopiperidin-3-yl)-7-methyl-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile **A124**;

3-(2-{4-hydroxy-1-[(1*H*-pyrazol-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A125**;

3-(2-{4-hydroxy-1-[(1,3-oxazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A126**;

3-(2-{4-hydroxy-1-[(1*H*-1,2,4-triazol-3-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A127**;

3-(2-{4-hydroxy-1-[(pyridin-3-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A128**;

3-(2-{4-hydroxy-1-[(pyridin-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A129**;

3-(2-{4-hydroxy-1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A130**;

3-(2-{4-hydroxy-1-[(1,3-thiazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A131**;

3-(2-{4-hydroxy-1-[(piperidin-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A132**;

3-(2-{4-hydroxy-1-[(oxan-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A133**;

3-(2-{4-hydroxy-1-[(oxan-3-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A134**;

3-(2-{4-hydroxy-1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A135**;

3-{2-[1-(2-azaspiro[3.3]heptan-6-yl)methyl]-4-hydroxypiperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A136**;

3-(2-{4-hydroxy-1-[(5-methyl-1,3-thiazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A137**;

3-[2-(4-hydroxy-1-{[(1*r*,4*r*)-4-aminocyclohexyl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A138**;

3-{2-[4-hydroxy-1-(5*H*,6*H*,7*H*-pyrrolo[1,2-*a*]imidazol-2-yl)methyl]piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A139**;

3-(2-{4-hydroxy-1-[(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A140**;

3-[2-(4-hydroxy-1-{[1-(propan-2-yl)-1*H*-pyrazol-4-yl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A141**;

3-{2-[4-hydroxy-1-(imidazo[1,2-*a*]pyridin-2-yl)methyl]piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A142**;

3-{2-[4-hydroxy-1-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl]piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A143**;

3-(2-{1-[(1,3-benzoxazol-2-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A144**;

3-{2-[4-hydroxy-1-([1,2,4]triazolo[1,5-*a*]pyridin-7-yl)methyl]piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A145**;

- 3-(2-{1-[(2,3-dihydro-1*H*-isoindol-5-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A146**;
- 3-{2-[4-hydroxy-1-({4*H*,5*H*,6*H*,7*H*-pyrazolo[1,5-*a*]pyridin-3-yl)methyl]-piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A147**;
- 3-{2-[1-({4*H*,5*H*,6*H*-cyclopenta[*d*][1,3]thiazol-2-yl)methyl]-4-hydroxypiperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A148**;
- 3-{2-[1-({2-azaspiro[3.5]nonan-7-yl)methyl]-4-hydroxypiperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A149**;
- 3-(2-{1-[(1-acetyl)piperidin-4-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A150**;
- 3-[2-(4-hydroxy-1-{[1-(propan-2-yl)piperidin-4-yl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A151**;
- 3-(2-{4-hydroxy-1-[(quinolin-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A152**;
- 3-(2-{4-hydroxy-1-[(3-oxo-2,3-dihydro-1*H*-isoindol-5-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A153**;
- 3-[(4-{6-[2,6-dioxopiperidin-3-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-2-yl}-4-hydroxypiperidin-1-yl)methyl]-*N*-methylbenzamide **A154**;
- 3-(2-{1-[(1,3-benzothiazol-2-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A155**;
- 3-[2-(4-hydroxy-1-{[4-(2-hydroxyethoxy)phenyl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A156**;
- 3-[2-(4-hydroxy-1-{[4-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A157**;
- 3-(2-{4-hydroxy-1-[(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)methyl]-piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A158**;
- 3-{2-[4-hydroxy-1-({4-methyl-2*H*,3*H*,4*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)methyl]-piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A159**;
- 3-{2-[1-({3-azaspiro[5.5]undecan-9-yl)methyl]-4-hydroxypiperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A160**;

4-[(4-{6-[2,6-dioxopiperidin-3-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-2-yl}-4-hydroxypiperidin-1-yl)methyl]benzene-1-sulfonamide **A161**;

3-(2-{4-hydroxy-1-[(5-methyl-1*H*-pyrazol-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A162**;

3-(2-{4-hydroxy-1-[(5-methyl-1,3,4-thiadiazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A163**;

3-[2-(4-hydroxy-1-{[1-(propan-2-yl)-1*H*-pyrazol-3-yl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A164**;

3-{2-[4-hydroxy-1-({1*H*-pyrrolo[3,2-*b*]pyridin-2-yl}methyl)piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A165**;

3-{2-[4-hydroxy-1-({5*H*,6*H*,7*H*,8*H*-imidazo[1,2-*a*]pyridin-2-yl}methyl)piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A166**;

3-[2-(4-hydroxy-1-{[4-(piperidin-4-yloxy)phenyl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A167**;

3-(2-{1-[(1-benzylpiperidin-4-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A168**; or

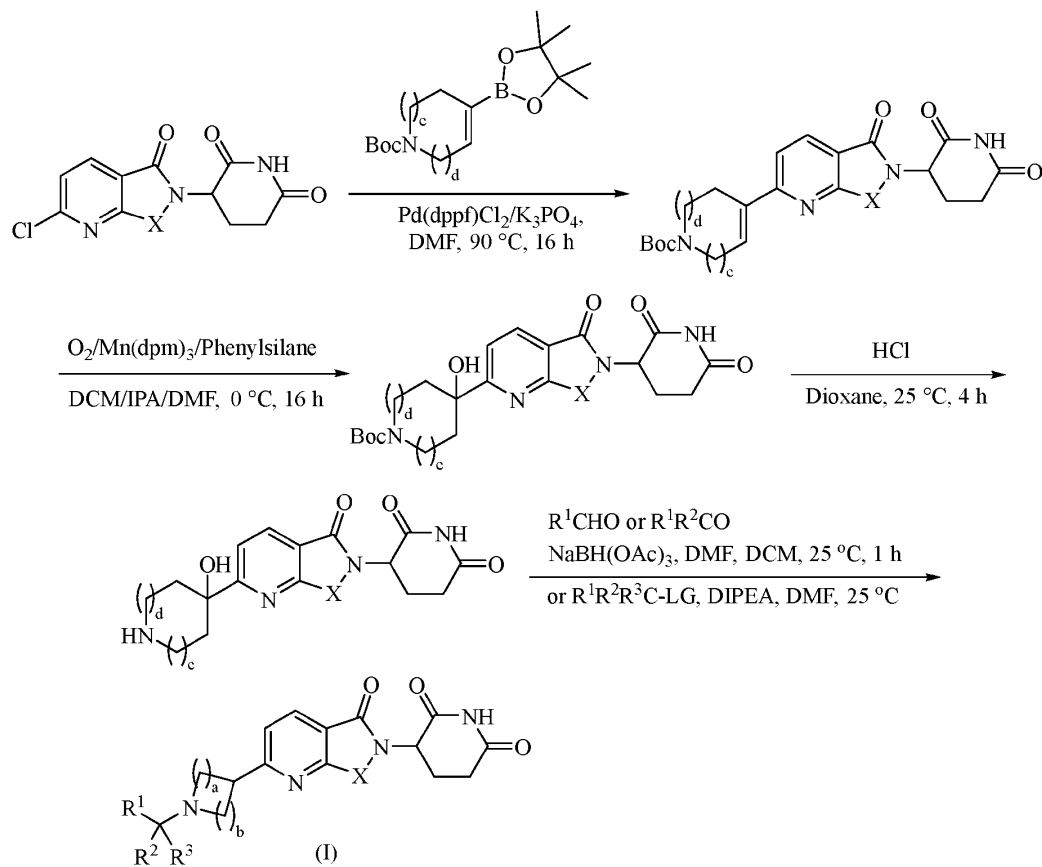
3-(2-{4-hydroxy-1-[(quinolin-3-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A169**;

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

III. SYNTHESIS OF THE COMPOUNDS

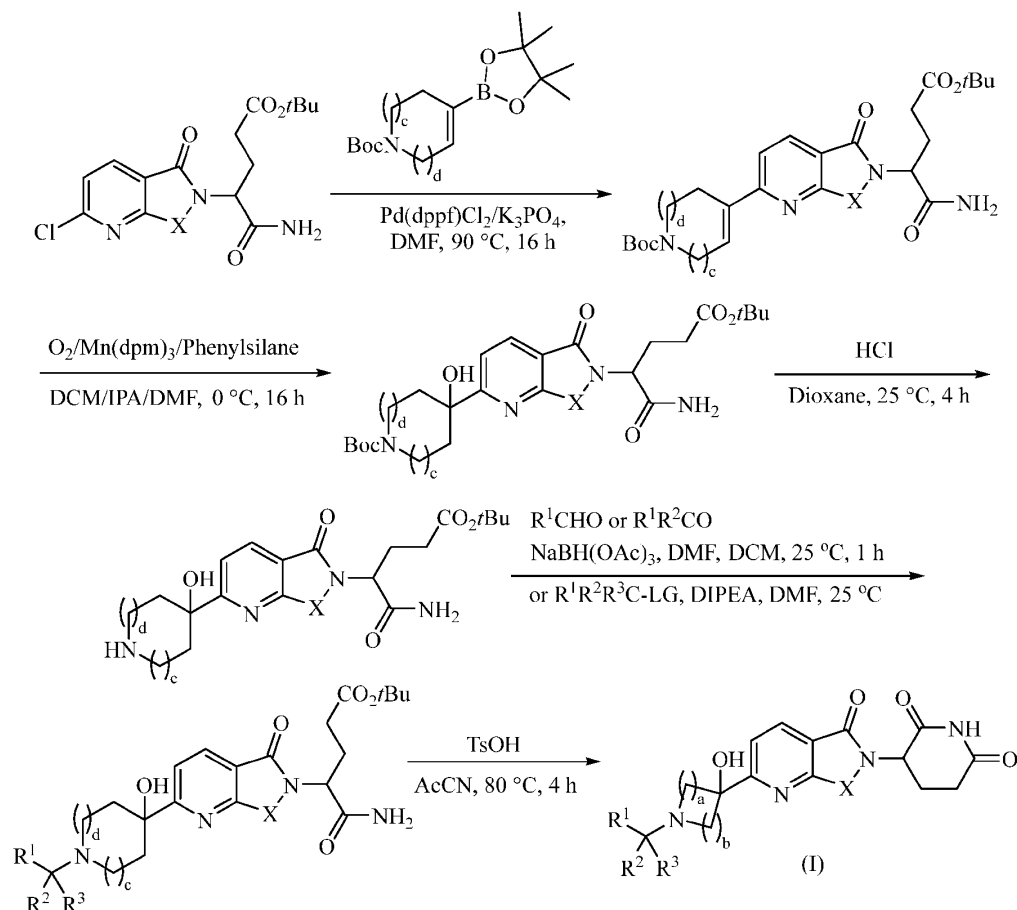
[0221] The compounds provided herein can be synthesized using methods well known to those of skill in the art. In one embodiment, a compound provided herein is prepared as shown in Scheme I, where R¹, R², R³, X, a, b, c, and d are each as defined herein; and LG is a leaving group, *e.g.*, chloro, bromo, iodo, or tosyloxy.

Scheme I



[0222] In another embodiment, a compound provided herein is prepared as shown in Scheme II, where R^1 , R^2 , R^3 , X, LG, a, b, c, and d are each as defined herein.

Scheme II



IV. PHARMACEUTICAL COMPOSITIONS

[0223] The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of compounds provided herein and a pharmaceutically acceptable carrier, diluent, or excipient.

[0224] The compounds can be formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for ophthalmic or parenteral administration, as well as transdermal patch preparation and dry powder inhalers. Typically, the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art. *See, e.g., Pharmaceutical*

Dosage Forms and Drug Delivery Systems, 7th ed.; Ansel *et al.*, Ed.; Lippincott Williams & Williams, 1999.

[0225] In the compositions, effective concentrations of one or more compounds or pharmaceutically acceptable salts are mixed with a suitable pharmaceutical carrier or vehicle. In certain embodiments, the concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms and/or progression of a disease or disorder disclosed herein.

[0226] Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

[0227] In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients. Liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as known in the art. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

[0228] The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the subject treated. The therapeutically effective concentration may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein and then extrapolated therefrom for dosages for humans. In some embodiments, the active compound is administered in a method to achieve a therapeutically effective concentration of the drug. In some embodiments, a companion diagnostic is used to determine the therapeutic concentration

and safety profile of the active compound in specific subjects or subject populations. Olsen and Jorgensen, *Front. Oncol.* **2014**, *4*, 105.

[0229] The concentration of active compound in the pharmaceutical composition will depend on absorption, tissue distribution, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of a disease or disorder disclosed herein.

[0230] In certain embodiments, a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/mL to about 50-100 µg/mL. In one embodiment, the pharmaceutical compositions provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 1,000 mg and in certain embodiments, from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

[0231] The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[0232] Thus, effective concentrations or amounts of one or more of the compounds described herein or pharmaceutically acceptable salts thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. Compounds are included in an amount effective for ameliorating one or more symptoms of, or for treating, retarding progression, or preventing. The concentration of active compound in the composition will depend on absorption, tissue distribution, inactivation,

excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

[0233] The compositions are intended to be administered by a suitable route, including, but not limited to, oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, intrathecal, mucosal, dermal, transdermal, buccal, rectal, topical, local, nasal or inhalation. For oral administration, capsules and tablets can be formulated. The compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration.

[0234] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerin, propylene glycol, dimethyl acetamide or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, pens, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

[0235] In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethyl sulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate.

[0236] Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

[0237] The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable salts thereof. The pharmaceutically therapeutically active compounds and salts thereof are formulated and administered in unit dosage forms or multiple dosage forms. Unit dose forms as used herein

refer to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit dose forms include ampules and syringes and individually packaged tablets or capsules. Unit dose forms may be administered in fractions or multiples thereof. A multiple dose form is a plurality of identical unit dosage forms packaged in a single container to be administered in segregated unit dose form. Examples of multiple dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit doses which are not segregated in packaging.

[0238] Sustained-release preparations can also be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the compound provided herein, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsule. Examples of sustained-release matrices include iontophoresis patches, polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated compound remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37 °C, resulting in a loss of biological activity and possible changes in their structure. Rational strategies can be devised for stabilization depending on the mechanism of action involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

[0239] Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the

incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium croscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain about 0.001%-100% active ingredient, in certain embodiments, about 0.1-85% active ingredient, or, in other embodiments, about 75-95% active ingredient.

[0240] The active compounds or pharmaceutically acceptable salts may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings.

[0241] The compositions may include other active compounds to obtain desired combinations of properties. The compounds provided herein, or pharmaceutically acceptable salts thereof as described herein, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as diseases related to oxidative stress. It is to be understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

[0242] Lactose-free compositions provided herein can contain excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopeia (USP) SP (XXI)/NF (XVI). In general, lactose-free compositions contain an active ingredient, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Exemplary lactose-free dosage forms contain an active ingredient, microcrystalline cellulose, pre-gelatinized starch and magnesium stearate.

[0243] Further encompassed are anhydrous pharmaceutical compositions and dosage forms containing a compound provided herein. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a

formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment and use of formulations.

[0244] Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[0245] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs and strip packs.

A. ORAL DOSAGE FORMS

[0246] Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric coated, sugar coated or film coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

[0247] In certain embodiments, the formulations are solid dosage forms, such as capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

[0248] Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include croscarmellose sodium, sodium starch glycolate, crospovidone, alginic acid, corn starch, potato

starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water-soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Emetic coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[0249] If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

[0250] When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[0251] The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H₂ blockers, and diuretics. The active ingredient is a compound or pharmaceutically acceptable salt thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

[0252] Pharmaceutically acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric coated tablets, because of the enteric coating, resist the action of stomach acid and dissolve or

disintegrate in the neutral or alkaline intestines. Sugar coated tablets are compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar coated, multiple compressed and chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[0253] Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil in-water or water in oil. In some embodiments, the suspension is a suspension of microparticles or nanoparticles. In some embodiments, the emulsion is an emulsion of microparticles or nanoparticles.

[0254] Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

[0255] Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and

sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic adds include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water-soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

[0256] For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, *e.g.*, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be easily measured for administration.

[0257] Alternatively, liquid or semi solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxyethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxy-toluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

[0258] Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

[0259] In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

B. INJECTABLES, SOLUTIONS AND EMULSIONS

[0260] Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. In some embodiments, the suspension is a suspension of microparticles or nanoparticles. In some embodiments, the emulsion is an emulsion of microparticles or nanoparticles. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. Implantation of a slow release or sustained release system, such that a constant level of dosage is maintained is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene-terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of

active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

[0261] Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[0262] If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[0263] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

[0264] Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl *p*-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[0265] The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the subject or animal as is known in the art.

[0266] The unit dose parenteral preparations are packaged in an ampule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

[0267] Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

[0268] Injectables are designed for local and systemic administration. Typically, a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, such as more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

[0269] The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

C. LYOPHILIZED POWDERS

[0270] Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

[0271] The sterile, lyophilized powder is prepared by dissolving a compound provided herein, or a pharmaceutically acceptable salt thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Generally, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage (including, but not limited to, 10-1,000 mg or 100-500 mg) or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature.

[0272] Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, about 1-50 mg, about 5-35 mg, or about 9-30 mg of lyophilized powder, is added per mL of sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

D. TOPICAL ADMINISTRATION

[0273] Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsion or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[0274] The compounds or pharmaceutically acceptable salts thereof may be formulated as aerosols for topical application, such as by inhalation (*see, e.g.*, U.S. Pat. Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment

of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will have diameters of less than 50 microns or less than 10 microns.

[0275] The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

[0276] These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01%-10% isotonic solutions, pH about 5-7, with appropriate salts.

E. COMPOSITIONS FOR OTHER ROUTES OF ADMINISTRATION

[0277] Other routes of administration, such as topical application, transdermal patches, and rectal administration are also contemplated herein.

[0278] For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein to mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono, di and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. An exemplary weight of a rectal suppository is about 2 to 3 grams.

[0279] Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

F. SUSTAINED RELEASE COMPOSITIONS

[0280] Active ingredients provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and U.S. Pat. Nos. 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, 5,639,480, 5,733,566, 5,739,108, 5,891,474, 5,922,356, 5,972,891, 5,980,945, 5,993,855, 6,045,830, 6,087,324, 6,113,943, 6,197,350, 6,248,363, 6,264,970, 6,267,981, 6,376,461, 6,419,961, 6,589,548, 6,613,358, 6,699,500 and 6,740,634. Such dosage forms can be used to provide slow- or controlled-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients provided herein.

[0281] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. In one embodiment, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. In certain embodiments, advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased subject compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[0282] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

[0283] In certain embodiments, the agent may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump may be used. *See, e.g.,* Buchwald *et al.*, *Surgery* **1980**, 88, 507-16; Sefton, *Crit. Ref. Biomed. Eng.* **1987**, 14, 201-40; Saudek *et al.*, *N. Engl. J. Med.* **1989**, 321, 574-9. In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity to the therapeutic target, *i.e.*, thus requiring only a fraction of the systemic dose.

[0284] In certain embodiments, a controlled release device is introduced into a subject in proximity to the site of inappropriate immune activation or a tumor. Other controlled release systems are discussed in the review by Langer (*Science* **1990**, 249, 1527-33). The active ingredient can be dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The active ingredient then diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active ingredient contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

G. TARGETED FORMULATIONS

[0285] The compounds provided herein, or pharmaceutically acceptable salts thereof, may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Many such targeting methods are well known to those of skill in the art. All such

targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, *see, e.g.*, U.S. Pat. Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751, 6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674, 5,759,542, and 5,709,874.

[0286] In one embodiment, liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Pat. No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

H. ARTICLES OF MANUFACTURE

[0287] The compounds or pharmaceutically acceptable salts can be packaged as articles of manufacture containing packaging material, a compound or pharmaceutically acceptable salt thereof provided herein, which is used for treatment, prevention or amelioration of one or more symptoms or progression of a disease or disorder disclosed herein, and a label that indicates that the compound or pharmaceutically acceptable salt thereof is used for treatment, prevention or amelioration of one or more symptoms or progression of a disease or disorder disclosed herein.

[0288] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. *See, e.g.*, U.S. Pat. Nos. 5,323,907, 5,052,558, and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, pens, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated.

[0289] In certain embodiments, provided herein also are kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a subject. In certain embodiments, the kit provided herein includes a container and a dosage form

of a compound provided herein, including a single enantiomer or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0290] In certain embodiments, the kit includes a container comprising a dosage form of the compound provided herein, including a single enantiomer or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a container comprising one or more other therapeutic agent(s) described herein.

[0291] Kits provided herein can further include devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, needle-less injectors drip bags, patches, and inhalers. The kits provided herein can also include condoms for administration of the active ingredients.

[0292] Kits provided herein can further include pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: aqueous vehicles, including, but not limited to, Water for Injection USP, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles, including, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles, including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

V. DOSING

[0293] The compounds and pharmaceutical compositions provided herein may be dosed in certain therapeutically or prophylactically effective amounts, certain time intervals, certain dosage forms, and certain dosage administration methods as described herein.

[0294] In certain embodiments, a therapeutically or prophylactically effective amount of the compound provided herein is from about 0.005 to about 1,000 mg per day, from about 0.01 to about 500 mg per day, from about 0.01 to about 250 mg per day, from about 0.01 to about 100 mg per day, from about 0.1 to about 100 mg per day, from about 0.5 to about 100 mg per day, from about 1 to about 100 mg per day, from about 0.01 to about 50 mg per day, from about 0.1 to about 50 mg per day, from about 0.5 to about 50 mg per day, from about 1 to about 50 mg per

day, from about 0.02 to about 25 mg per day, from about 0.05 to about 10 mg per day, from about 0.05 to about 5 mg per day, from about 0.1 to about 5 mg per day, or from about 0.5 to about 5 mg per day.

[0295] In certain embodiments, the therapeutically or prophylactically effective amount of the compound provided herein is about 0.1, about 0.2, about 0.5, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 15, about 20, about 25, about 30, about 40, about 45, about 50, about 60, about 70, about 80, about 90, about 100, or about 150 mg per day.

[0296] In certain embodiments, the recommended daily dose range of the compound provided herein or a derivative thereof for the conditions described herein lie within the range of from about 0.5 mg to about 50 mg per day, given as a single once-a-day dose or in divided doses throughout a day. In certain embodiments, the daily dosage ranges from about 1 mg to about 50 mg per day. In certain embodiments, the daily dosage ranges from about 0.5 to about 5 mg per day. Specific doses per day include 0.1, 0.2, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 mg per day.

[0297] In certain embodiments, the recommended starting dosage is 0.5, 1, 2, 3, 4, 5, 10, 15, 20, 25, or 50 mg per day. In certain embodiments, the recommended starting dosage may be 0.5, 1, 2, 3, 4, or 5 mg per day. In certain embodiments, the dose is escalated to 15, 20, 25, 30, 35, 40, 45, and 50 mg/day. In certain embodiments, the compound provided herein is administered in an amount of about 25 mg/day. In certain embodiments, the compound provided herein is administered in an amount of about 10 mg/day. In certain embodiments, the compound provided herein is administered in an amount of about 5 mg/day. In certain embodiments, the compound provided herein is administered in an amount of about 4 mg/day. In certain embodiments, the compound provided herein is administered in an amount of about 3 mg/day.

[0298] In certain embodiments, the therapeutically or prophylactically effective amount is from about 0.001 to about 100 mg/kg/day, from about 0.01 to about 50 mg/kg/day, from about 0.01 to about 25 mg/kg/day, from about 0.01 to about 10 mg/kg/day, from about 0.01 to about 9 mg/kg/day, 0.01 to about 8 mg/kg/day, from about 0.01 to about 7 mg/kg/day, from about 0.01 to about 6 mg/kg/day, from about 0.01 to about 5 mg/kg/day, from about 0.01 to about 4

mg/kg/day, from about 0.01 to about 3 mg/kg/day, from about 0.01 to about 2 mg/kg/day, from about 0.01 to about 1 mg/kg/day, or from about 0.01 to about 0.05 mg/kg/day.

[0299] The administered dose can also be expressed in units other than mg/kg/day. For example, doses for parenteral administration can be expressed as mg/m²/day. One of ordinary skill in the art would readily know how to convert doses from mg/kg/day to mg/m²/day to given either the height or weight of a subject or both. For example, a dose of 1 mg/kg/day for a 65 kg human is approximately equal to 38 mg/m²/day.

[0300] In certain embodiments, the amount of the compound administered is sufficient to provide a plasma concentration of the compound at steady state, ranging from about 0.001 to about 500 μM, about 0.002 to about 200 μM, about 0.005 to about 100 μM, about 0.01 to about 50 μM, from about 1 to about 50 μM, about 0.02 to about 25 μM, from about 0.05 to about 20 μM, from about 0.1 to about 20 μM, from about 0.5 to about 20 μM, or from about 1 to about 20 μM.

[0301] In certain embodiments, the amount of the compound administered is sufficient to provide a plasma concentration of the compound at steady state, ranging from about 5 to about 100 nM, about 5 to about 50 nM, about 10 to about 100 nM, about 10 to about 50 nM, or from about 50 to about 100 nM.

[0302] As used herein, the term "plasma concentration at steady state" is the concentration reached after a period of administration of a compound provided herein or a derivative thereof. Once steady state is reached, there are minor peaks and troughs on the time dependent curve of the plasma concentration of the compound.

[0303] In certain embodiments, the amount of the compound administered is sufficient to provide a maximum plasma concentration (peak concentration) of the compound, ranging from about 0.001 to about 50 μM, about 0.002 to about 200 μM, about 0.005 to about 100 μM, about 0.01 to about 50 μM, from about 1 to about 50 μM, about 0.02 to about 25 μM, from about 0.05 to about 20 μM, from about 0.1 to about 20 μM, from about 0.5 to about 20 μM, or from about 1 to about 20 μM.

[0304] In certain embodiments, the amount of the compound administered is sufficient to provide a minimum plasma concentration (trough concentration) of the compound, ranging from about 0.001 to about 500 μM, about 0.002 to about 200 μM, about 0.005 to about 100 μM, about 0.01 to about 50 μM, from about 1 to about 50 μM, about 0.01 to about 25 μM, from about 0.01

to about 20 μ M, from about 0.02 to about 20 μ M, from about 0.02 to about 20 μ M, or from about 0.01 to about 20 μ M.

[0305] In certain embodiments, the amount of the compound administered is sufficient to provide an area under the curve (AUC) of the compound, ranging from about 100 to about 100,000 ng*hr/mL, from about 1,000 to about 50,000 ng*hr/mL, from about 5,000 to about 25,000 ng*hr/mL, or from about 5,000 to about 10,000 ng*hr/mL.

[0306] The methods provided herein encompass treating a patient regardless of subject's age, although some diseases or disorders are more common in certain age groups.

[0307] Depending on the disease to be treated and the subject's condition, the compound provided herein or a derivative thereof may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, CIV, intracisternal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (*e.g.*, transdermal or local) routes of administration. The compound provided herein or a derivative thereof may be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants and vehicles, appropriate for each route of administration.

[0308] In one embodiment, the compound provided herein or a derivative thereof is administered orally. In another embodiment, the compound provided herein or a derivative thereof is administered parenterally. In yet another embodiment, the compound provided herein or a derivative thereof is administered intravenously.

[0309] The compound provided herein or a derivative thereof can be delivered as a single dose such as, *e.g.*, a single bolus injection, or oral tablets or pills; or over time, such as, *e.g.*, continuous infusion over time or divided bolus doses over time. The compound can be administered repeatedly if necessary, for example, until the subject experiences stable disease or regression, or until the subject experiences disease progression or unacceptable toxicity. For example, stable disease for solid tumors generally means that the perpendicular diameter of measurable lesions has not increased by 25% or more from the last measurement. Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines (*J. Nat'l Cancer Inst.* **2000**, 92, 205-16). Stable disease or lack thereof is determined by methods known in the art such as evaluation of patient symptoms, physical examination, visualization of the tumor that has been imaged using X-ray, CAT, PET, or MRI scan and other commonly accepted evaluation modalities.

[0310] The compound provided herein or a derivative thereof can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), three times daily (TID), and four times daily (QID). In addition, the administration can be continuous (*i.e.*, daily for consecutive days or every day), intermittent, *e.g.*, in cycles (*i.e.*, including days, weeks, or months of rest without drug). As used herein, the term "daily" is intended to mean that a therapeutic compound, such as the compound provided herein or a derivative thereof is administered once or more than once each day, for example, for a period of time. The term "continuous" is intended to mean that a therapeutic compound, such as the compound provided herein or a derivative thereof, is administered daily for an uninterrupted period of at least 10 days to 52 weeks. The term "intermittent" or "intermittently" as used herein is intended to mean stopping and starting at either regular or irregular intervals. For example, intermittent administration of the compound provided herein or a derivative thereof is administration for one to six days per week, administration in cycles (*e.g.*, daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week), or administration on alternate days. The term "cycling" as used herein is intended to mean that a therapeutic compound, such as the compound provided herein or a derivative thereof, is administered daily or continuously but with a rest period. In some such embodiments, administration is once a day for two to six days, then a rest period with no administration for five to seven days.

[0311] In certain embodiments, the frequency of administration is in the range of about a daily dose to about a monthly dose. In certain embodiments, administration is once a day, twice a day, three times a day, four times a day, once every other day, twice a week, once every week, once every two weeks, once every three weeks, or once every four weeks. In one embodiment, the compound provided herein or a derivative thereof is administered once a day. In another embodiment, the compound provided herein or a derivative thereof is administered twice a day. In yet another embodiment, the compound provided herein or a derivative thereof is administered three times a day. In still another embodiment, the compound provided herein or a derivative thereof is administered four times a day.

[0312] In certain embodiments, the compound provided herein or a derivative thereof is administered once per day from one day to six months, from one week to three months, from one week to four weeks, from one week to three weeks, or from one week to two weeks. In certain

embodiments, the compound provided herein or a derivative thereof is administered once per day for one week, two weeks, three weeks, or four weeks. In one embodiment, the compound provided herein or a derivative thereof is administered once per day for 4 days. In another embodiment, the compound provided herein or a derivative thereof is administered once per day for 5 days. In yet another embodiment, the compound provided herein or a derivative thereof is administered once per day for 6 days. In yet another embodiment, the compound provided herein or a derivative thereof is administered once per day for one week. In yet another embodiment, the compound provided herein or a derivative thereof is administered once per day for two weeks. In yet another embodiment, the compound provided herein or a derivative thereof is administered once per day for three weeks. In still another embodiment, the compound provided herein or a derivative thereof is administered once per day for four weeks.

VI. METHODS OF TREATMENT

[0313] In one embodiment, provided herein is a method of treating, preventing, or ameliorating one or more symptoms of a disease or disorder in which ARNT is overexpressed and/or in which ARNT activity is not desired and/or in which ARNT acts as a factor in pro-oncogenic activity.

[0314] In another embodiment, provided herein is a method of treating, preventing, or ameliorating one or more symptoms of an ARNT-mediated disease or disorder in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound provided herein, *e.g.*, a compound of Formula (A) or (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof.

[0315] In certain embodiments, the ARNT-mediated disease or disorder is cancer.

[0316] In another embodiment, provided herein is a method of treating, preventing, or ameliorating one or more symptoms of cancer in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound provided herein, *e.g.*, a compound of Formula (A) or (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof.

[0317] In yet another embodiment, provided herein is a method of inhibiting the growth of a cell, comprising contacting the cell with an effective amount of a compound provided herein, *e.g.*, a compound of Formula (A) or (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof.

[0318] In certain embodiments, the cell is a cancerous cell.

[0319] In still another embodiment, provided herein is a method of inducing degradation of an ARNT, comprising contacting the ARNT with an effective amount of a compound provided herein, *e.g.*, a compound of Formula (A) or (I), or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof.

VII. COMBINATION THERAPY WITH A SECOND THERAPEUTIC AGENT

[0320] The compound provided herein or a derivative thereof can be used in combination with a second therapeutic agent useful in the treatment and/or prevention of a disease or disorder in which ARNT is overexpressed and/or in which ARNT activity is not desired and/or in which ARNT acts as a factor in pro-oncogenic activity.

[0321] In one embodiment, provided herein is a method of treating, preventing, or managing cancer, comprising administering to a subject a compound provided herein or a derivative thereof in combination with a second therapeutic agent.

[0322] As used herein, the term "in combination" includes the use of more than one therapy (*e.g.*, one or more prophylactic and/or therapeutic agents). However, the use of the term "in combination" does not restrict the order in which therapies (*e.g.*, prophylactic and/or therapeutic agents) are administered. A first therapy (*e.g.*, a prophylactic or therapeutic agent such as a compound provided herein or a derivative thereof) can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the

administration of a second therapy (*e.g.*, a prophylactic or therapeutic agent). Triple therapy is also contemplated herein.

[0323] Administration of the compound provided herein or a derivative thereof and a second therapeutic agent can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular therapeutic agent will depend on the active agent itself (*e.g.*, whether it can be administered orally without decomposing prior to entering the blood stream) and the disease or disorder being treated.

[0324] The route of administration of the compound provided herein or a derivative thereof is independent of the route of administration of a second therapy. In one embodiment, the compound provided herein or a derivative thereof is administered orally. In another embodiment, the compound provided herein or a derivative thereof is administered intravenously. Thus, in accordance with these embodiments, the compound provided herein or a derivative thereof is administered orally or intravenously, and the second therapy can be administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, *via* inhalation, vaginally, intraocularly, *via* local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form. In one embodiment, the compound provided herein or a derivative thereof, and a second therapy are administered by the same mode of administration, orally or by IV. In another embodiment, the compound provided herein or a derivative thereof is administered by one mode of administration, *e.g.*, by IV, whereas the second agent is administered by another mode of administration, *e.g.*, orally.

[0325] In one embodiment, the second active agent is administered intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1,000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount of the compound provided herein or a derivative thereof, and any optional additional active agents concurrently administered to the subject.

VIII. EXAMPLES

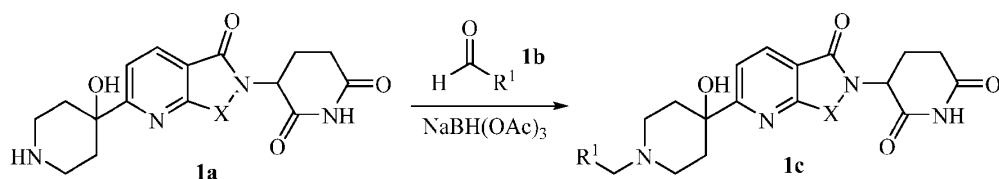
[0326] The examples below are meant to illustrate certain embodiments provided herein, and not to limit the scope of this disclosure.

[0327] As used herein, the symbols and conventions used in these processes, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society, the Journal of Medicinal Chemistry, or the Journal of Biological Chemistry. Specifically, but without limitation, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); mL (milliliters); μ L (microliters); mM (millimolar); μ M (micromolar); mmol (millimoles); min (minute or minutes); h (hour or hours); ACN (acetonitrile); AcOH (acetic acid); AIBN (azobisisobutyronitrile); BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl); Boc (*tert*-butoxycarbonyl); *t*Bu (*tert*-butyl); *t*BuOH (*tert*-butanol); Cbz (benzyloxycarbonyl); DCE (dichloroethane); DCM (dichloromethane); DIBAL-H (diisobutylaluminum hydride); DIPEA (*N,N*-diisopropylethylamine); DMAP (4-dimethylamino-pyridine); DME (dimethyl ether); DMF (dimethylformamide); DMSO (dimethyl sulfoxide); EtOAc (ethyl acetate); EtOH (ethanol); FA (formic acid); HATU (hexafluorophosphate azabenzotriazole tetramethyl uronium); IPA (isopropanol); MeOH (methanol); MsNH₂ (methanesulfonamide); MTBE (methyl *tert*-butylether); NaBH(OAc)₃ (sodium triacetoxyborohydride); Mn(dpm)₃ (tris(2,2,6,6-tetramethyl-3,5-heptanedionato)-manganese(III)); NaBH(OAc)₃ (sodium triacetoxyborohydride); NBS (*N*-bromosuccinimide); NiCl₂·dtbpy ((4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine) nickel (II) dichloride); Pd₂(dppf)Cl₂ ((1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II)); Pd(OAc)₂ (palladium acetate); PE (petroleum ether); SO₃·Py (sulfur trioxide pyridine complex); TEA (triethylamine); TFA (trifluoroacetic acid); TFE (tetrafluoroethylene); THF (tetrahydrofuran); TMSCF₃ (trifluoromethyltrimethylsilane); T₄P (3-(2,6,8-trioxo-9-((2*R*,3*R*,4*R*)-2,3,4,5-tetrahydroxypentyl)-3*H*-purin-7-yl)propyl dihydrogen phosphate); Ts (tosyl); TsCl (tosyl chloride); TsOH (tosylic acid); TTMS (tris(trimethylsilyl)silane); MS (mass spectrometry); NMR (nuclear magnetic resonance); prep-HPLC (preparative high performance liquid chromatography); SFC (supercritical fluid chromatography); and prep-TLC (preparative thin layer chromatography).

[0328] For all of the following examples, standard work-up and purification methods known to those skilled in the art can be utilized. Unless otherwise indicated, all temperatures are

expressed in °C (degrees Centigrade). All reactions are conducted at room temperature unless otherwise specified. Synthetic methodologies illustrated herein are intended to exemplify the applicable chemistry through the use of specific examples and are not indicative of the scope of the disclosure.

GENERAL REDUCTION AMINATION PROCEDURES



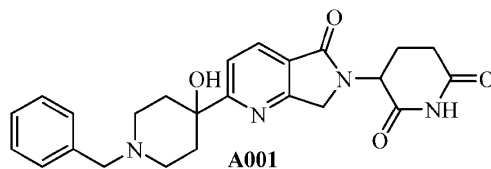
[0329] Procedure 1: To a solution of compound **1a** as a HCl salt (100 μ mol, 1 eq.) and compound **1b** (120 μ mol, 1.2 eq.) in DMF (0.5 mL) and DCM (0.5 mL) were added DIPEA (3 eq.) and NaBH(OAc)₃ (2 eq.). After stirring at 30 °C for 16 h, the reaction mixture was concentrated and purified by prep-HPLC to afford compound **1c**.

[0330] Procedure 2: To a solution of compound **1a** (100 μ mol, 1 eq.) and compound **1b** (120 μ mol, 1.2 eq.) in MeOH (1 mL) were added AcOH (300 μ mol, 3 eq.) and NaBH₃CN (200 μ mol, 2 eq.). After stirring at 50 °C for 16 h, the reaction mixture was concentrated and purified by prep-HPLC to afford compound **1c**.

[0331] Procedure 3: To a solution of compound **1a** (100 μ mol, 1 eq.) and compound **1b** (120 μ mol, 1.2 eq.) in MeOH (1 mL) were added AcOH (300 μ mol, 3 eq.) and NaBH₃CN (200 μ mol, 2 eq.). After stirring at 120 °C for 6 h under microwave, the reaction mixture was concentrated and purified by prep-HPLC to afford compound **1c**.

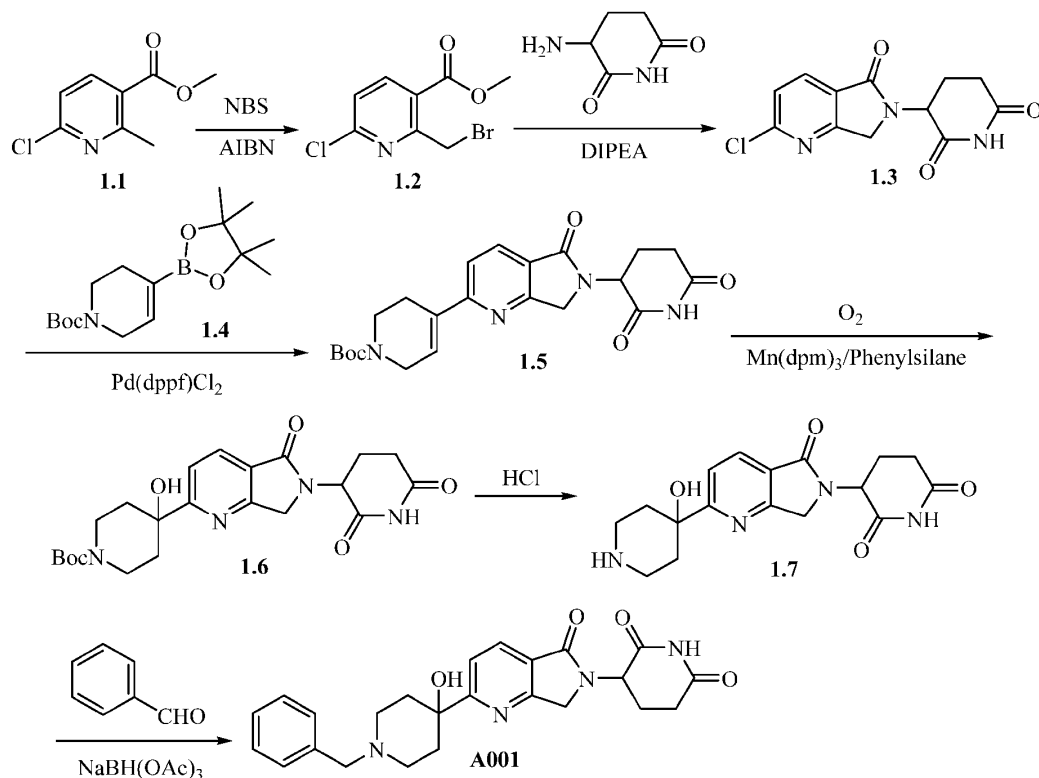
EXAMPLE 1

Synthesis of 3-(2-(1-benzyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A001**



[0332] Compound **A001** was prepared as shown in Scheme 1.

Scheme 1



[0333] Preparation of methyl 2-(bromomethyl)-6-chloronicotinate **1.2**. To a mixture of methyl 6-chloro-2-methylnicotinate **1.1** (25 g, 134 mmol) and AIBN (4.42 g, 26.9 mmol) in CCl₄ (120 mL) was added NBS (26.3 g, 148 mmol) under N₂. After stirring at 80 °C for 12 h under N₂, the reaction mixture was filtered, concentrated, and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **1.2** (30 g) in 50% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.26-8.24 (m, 1H), 7.38-7.36 (m, 1H), 4.98 (s, 2H), 3.98 (s, 3H); MS (ESI) *m/z*: 265.8 [M+H]⁺.

[0334] Preparation of 3-(2-chloro-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-piperidine-2,6-dione **1.3**. A mixture of compound **1.2** (30 g, 65.7 mmol), 3-aminopiperidine-2,6-dione as a HCl salt (10.8 g, 65.7 mmol), and DIPEA (25.5 g, 197 mmol) in DMF (300 mL) was stirred at 110 °C for 3 h under N₂. The reaction mixture was then diluted with H₂O (500 mL) and extracted with DCM (3 x 500 mL). The combined organic layers were washed with brine (3 x 500 mL), dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography (SiO₂, MeOH/DCM) to afford compound **1.3** (11 g) in 44% yield. ¹H NMR

(400 MHz, CDCl₃) δ 8.13-8.11 (m, 1H), 7.50-7.48 (m, 1H), 5.26-5.21 (m, 1H), 4.56-4.37 (m, 2H), 3.95 (s, 1H), 2.90-2.85 (m, 1H), 2.44-2.39 (m, 2H), 2.89-2.7 (m, 2H); MS (ESI) m/z : 279.9 [M+H]⁺.

[0335] Preparation of *tert*-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **1.5**. To a mixture of compound **1.3** (10 g, 35.7 mmol) in DMF (160 mL) were added *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **1.4** (16.5 g, 53.6 mmol), K₃PO₄ (9.11 g, 42.9 mmol), and Pd(dppf)Cl₂ (2.92 g, 3.58 mmol) under N₂. After stirring at 90 °C for 16 h under N₂, the reaction mixture was diluted with H₂O (600 mL) and extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (3 x 500 mL), dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography (SiO₂, MeOH/DCM) to afford compound **1.5** (3.8 g) in 24% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.12-8.10 (m, 1H), 7.72-7.70 (m, 1H), 6.88 (s, 1H), 5.19-5.15 (m, 1H), 4.53-4.31 (m, 2H), 4.09 (s, 2H), 3.57-3.54 (m, 2H), 2.97-2.88 (m, 1H), 2.62-2.60 (m, 4H), 2.04-2.01 (m, 1H), 1.43 (s, 9H); MS (ESI) m/z : 371.0 [M-55]⁺.

[0336] Preparation of *tert*-butyl 4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidine-1-carboxylate **1.6**. To a solution of compound **1.5** (1 g, 2.34 mmol) in DCM (12 mL), DMF (4 mL), and IPA (12 mL) at 0 °C were added phenylsilane (512 mg, 4.74 mmol) and Mn(dpm)₃ (709 mg, 1.17 mmol). After stirring at 0 °C for 16 h under O₂, the reaction was quenched with sat. aq. Na₂S₂O₃ (30 mL) and the reaction mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography (SiO₂, MeOH/DCM) to afford compound **1.6** (0.34 g) in 35% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.16-8.14 (m, 1H), 7.86-7.84 (m, 1H), 5.19-5.14 (m, 1H), 4.52-4.30 (m, 2H), 4.10-4.07 (m, 1H), 3.90-3.87 (m, 2H), 3.17-3.16 (m, 3H), 2.90-2.88 (m, 1H), 2.44-2.41 (m, 1H), 2.08-2.00 (m, 3H), 1.78-1.53 (m, 2H), 1.42 (s, 9H); MS (ESI) m/z : 389.1 [M-55]⁺.

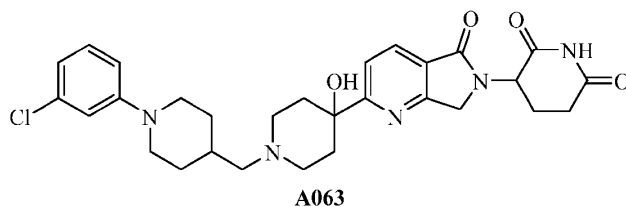
[0337] Preparation of 3-(2-(4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **1.7**. A solution of compound **1.6** (340 mg, 764 μ mol) in 4M HCl in dioxane (10 mL) was stirred under N₂ for 4 h. The reaction mixture was then filtered and concentrated to afford compound **1.7** as a HCl salt (280 mg) in 95% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.89-8.86 (m, 1H), 8.57-8.50 (m, 1H), 5.19-5.14 (m, 1H), 8.21-8.19

(m, 1H), 7.87-7.85 (m, 1H), 5.21-5.16 (m, 1H), 4.54-4.32 (m, 2H), 3.57 (s, 1H), 3.24-3.18 (m, 4H), 2.90-2.59 (m, 1H), 2.45-2.36 (m, 3H), 2.11-1.98 (m, 1H), 1.79-1.75 (m, 2H); MS (ESI) m/z : 345.1 $[M+H]^+$.

[0338] Preparation of 3-(2-(1-benzyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A001**. To a solution of compound **1.7** as a HCl salt (250 mg, 656 μ mol) in DCM (4 mL) and DMF (4 mL) were added benzaldehyde (90.5 mg, 853 μ mol) and NaBH(OAc)₃ (347 mg, 1.64 mmol) under N₂. After stirring for 1 h under N₂, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by prep-HPLC (C18, ACN/water containing 0.5% TFA) to afford compound **A001** (109 mg) in 37% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 9.56-9.55 (m, 1H), 8.21-8.19 (m, 1H), 7.87-7.85 (m, 1H), 7.58-7.56 (m, 2H), 7.51-7.49 (m, 3H), 5.98-5.93 (m, 1H), 5.20-5.16 (m, 1H), 4.52-4.31 (m, 4H), 3.35-3.28 (m, 4H), 2.93-2.63 (m, 1H), 2.60-2.51 (m, 1H), 2.45-2.40 (m, 3H), 2.21-1.98 (m, 1H), 1.84-1.82 (m, 2H); MS (ESI) m/z : 435.0 $[M+H]^+$.

EXAMPLE 2

Synthesis of 3-(2-(1-((1-(3-chlorophenyl)-4-piperidyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A063**

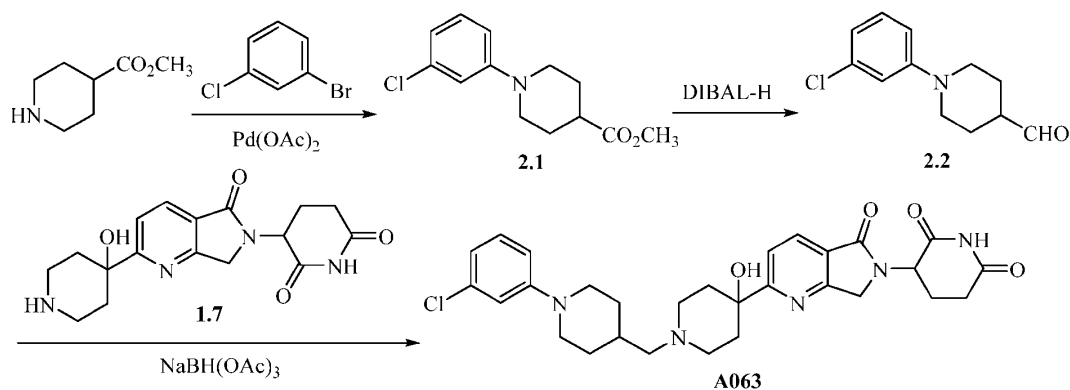


[0339] Compound **A063** was prepared as shown in Scheme 2.

[0340] Preparation of methyl 1-(3-chlorophenyl)piperidine-4-carboxylate **2.1**. To a solution of 1-bromo-3-chlorobenzene (3 g, 15.6 mmol) in dioxane (60 mL) were added methyl piperidine-4-carboxylate (2.24 g, 15.6 mmol), Cs₂CO₃ (10.2 g, 31.3 mmol), BINAP (1.46 g, 2.35 mmol), and Pd(OAc)₂ (527 mg, 2.35 mmol) under N₂. After stirring at 100 °C for 12 h under N₂, the reaction mixture was concentrated and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **2.1** (2.22 g) in 56% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.27-7.13 (m, 1H),

6.88 (d, $J = 2.4$ Hz, 1H), 6.81-6.78 (m, 2H), 3.71 (s, 3H), 3.66-3.61 (m, 2H), 2.85-2.78 (m, 2H), 2.51-2.43 (m, 1H), 2.04-2.00 (m, 2H), 1.90-1.84 (m, 2H); MS (ESI) m/z : 253.9 $[M+H]^+$.

Scheme 2



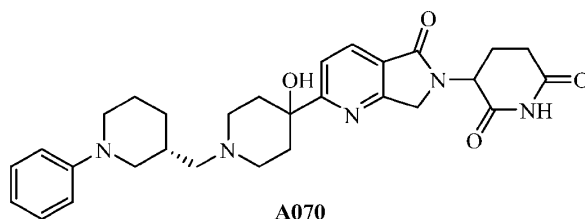
[0341] Preparation of 1-(3-chlorophenyl)piperidine-4-carbaldehyde **2.2**. To a solution of compound **2.1** (300 mg, 1.18 mmol) in toluene (6 mL) was added dropwise 1M DIBAL-H (1.18 mL) at -60 °C under N_2 . After stirring at -60 °C for 2 h under N_2 , the reaction was quenched by adding dropwise MeOH (5 mL) and brine (15 mL). After warming up to room temperature, the reaction mixture was filtered and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, concentrated, and purified by prep-TLC (SiO_2 , EtOAc/PE) to afford compound **2.2** (170 mg) in 62% yield. 1H NMR (400 MHz, $DMSO-d_6$) δ 9.62 (s, 1H), 7.18 (t, $J = 8.0$ Hz, 1H), 6.93-6.87 (m, 2H), 6.75-6.73 (m, 1H), 3.65-3.60 (m, 2H), 2.89-2.82 (m, 2H), 2.48-2.47 (m, 1H), 1.92-1.88 (m, 2H), 1.59-1.49 (m, 2H); MS (ESI) m/z : 242.0 $[M+18]^+$.

[0342] Preparation of 3-(2-(1-((1-(3-chlorophenyl)-4-piperidyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A063**. To a solution of compound **2.2** (70 mg, 304 μ mol) in DMF (1.5 mL) were added 3-(2-(4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **1.7** as a HCl salt (115 mg, 304 μ mol) and $NaBH(OAc)_3$ (193 mg, 912 μ mol). After stirring for 12 h, the reaction mixture was diluted with H_2O (0.5 mL) and purified by prep-HPLC (C18, ACN/water containing 0.225% FA) to afford compound **A063** (69 mg) in 40% yield. 1H NMR (400 MHz, $DMSO-d_6$) δ 11.01 (s, 1H), 8.15-8.13 (m, 2H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.18 (t, $J = 8.0$ Hz, 1H), 6.91-6.86 (m, 2H), 6.73-6.71 (s, 1H), 5.48-5.10 (m, 2H), 4.50 (d, $J = 18.0$ Hz, 1H), 4.33 (t, $J = 17.6$ Hz, 1H), 3.72 (d, $J = 12.8$ Hz, 2H), 2.97-2.88 (m, 1H), 2.79-2.77 (m, 2H), 2.72-2.59 (m, 3H), 2.47-2.38 (m, 3H), 2.32-

2.23 (m, 4H), 2.04-2.01 (m, 1H), 1.81-1.73 (m, 3H), 1.59-1.55 (m, 2H), 1.22-1.14 (m, 2H); MS (ESI) m/z : 552.3 $[M+H]^+$.

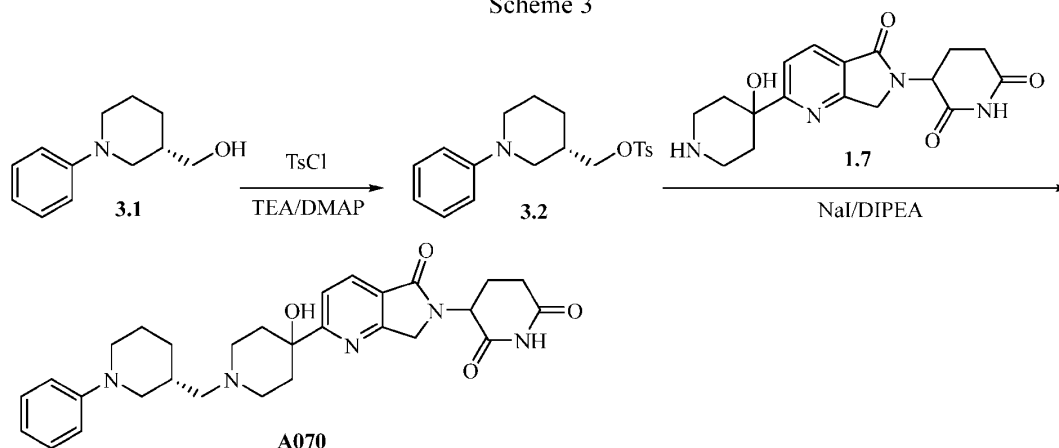
EXAMPLE 3

Synthesis of 3-(2-(4-hydroxy-1-(((*R*)-1-phenylpiperidin-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A070**



[0343] Compound **A070** was prepared as shown in Scheme 3.

Scheme 3

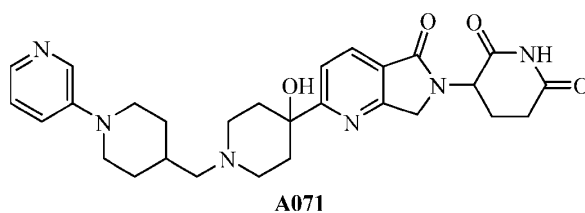


[0344] Preparation of ((3*S*)-1-phenyl-3-piperidyl)methyl 4-methylbenzenesulfonate **3.2**. To a solution of ((3*S*)-1-phenyl-3-piperidyl)methanol **3.1** (694 mg, 3.36 mmol) in DCM (14 mL) were added TEA (680 mg, 6.73 mmol), DMAP (20.5 mg, 168 μ mol), and TsCl (769 mg, 4.04 mmol). After stirring for 12 h, the reaction mixture was concentrated and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **3.2** (1.19 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.81 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.19-7.15 (m, 2H), 6.82 (d, J = 8.0 Hz, 2H), 6.74 (t, J = 7.6 Hz, 1H), 4.05-3.97 (m, 2H), 3.44-3.38 (m, 2H), 2.68-2.62 (m, 1H), 2.47-2.44 (m, 1H), 2.41 (s, 3H), 1.96-1.88 (m, 1H), 1.67-1.60 (m, 2H), 1.54-1.43 (m, 1H), 1.18-1.08 (m, 1H); MS (ESI) m/z : 346.0 $[M+H]^+$.

[0345] Preparation of 3-(2-(4-hydroxy-1-(((3*R*)-1-phenyl-3-piperidyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A070**. To a solution of compound **1.7** as a HCl salt (100 mg, 262 μ mol) in DMF (4 mL) were added DIPEA (169 mg, 1.31 mmol), compound **3.2** (272 mg, 787 μ mol), and NaI (196 mg, 1.31 mmol). After stirring at 80 °C for 12 h, the reaction mixture was diluted with DMF (1 mL) and purified by prep-HPLC (C18, ACN in water containing 10 mM NH_4HCO_3) to afford compound **A070** (34 mg) in 22% yield. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.26 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.21-7.17 (m, 2H), 6.90 (d, J = 7.6 Hz, 1H), 6.72 (t, J = 7.2 Hz, 1H), 5.19-5.14 (m, 1H), 4.54-4.48 (m, 1H), 4.36-4.31 (m, 1H), 3.66-3.63 (m, 1H), 3.56-3.53 (m, 1H), 2.97-2.92 (m, 1H), 2.75-2.58 (m, 4H), 2.46-2.37 (m, 3H), 2.33-2.18 (m, 5H), 2.05-2.00 (m, 1H), 1.90-1.69 (m, 3H), 1.62-1.50 (m, 3H), 1.14-1.04 (m, 2H). (ESI) m/z : 518.4 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 4

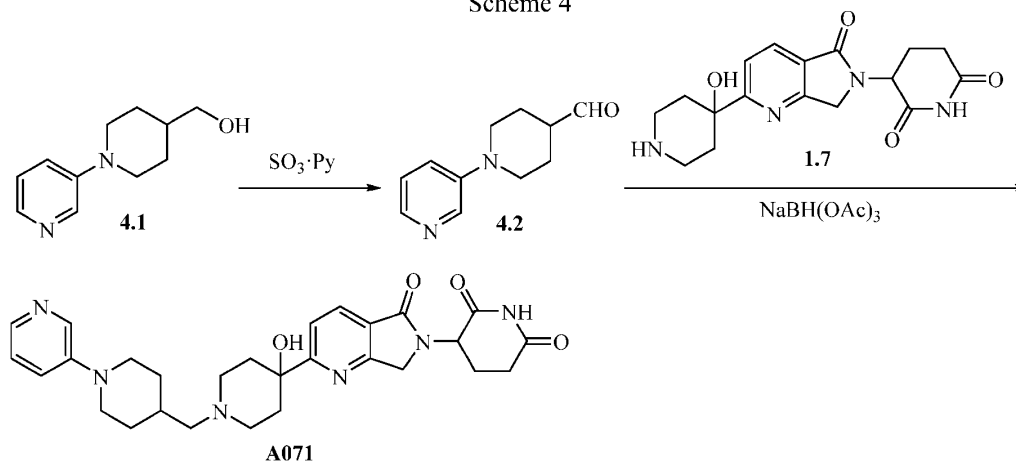
Synthesis of 3-(2-(4-hydroxy-1-((1-(pyridin-3-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A071**



[0346] Compound **A071** was prepared as shown in Scheme 4.

[0347] Preparation of 1-(pyridin-3-yl)piperidine-4-carbaldehyde **4.2**. To a solution of (1-(pyridin-3-yl)piperidin-4-yl)methanol **4.1** (250 mg, 1.3 mmol) in DCM (6 mL) and DMSO (1 mL) were added TEA (526 mg, 5.2 mmol) and SO₃·Py (414 mg, 2.6 mmol) at 0 °C. After stirring for 2 h, the reaction mixture was diluted with H₂O (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by prep-TLC (SiO₂, MeOH/DCM) to afford compound **4.2** (200 mg) in 81% yield. MS (ESI) *m/z*: 191.1 [M+H]⁺.

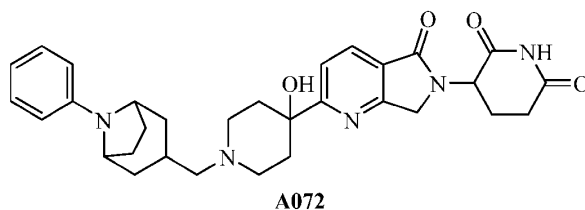
Scheme 4



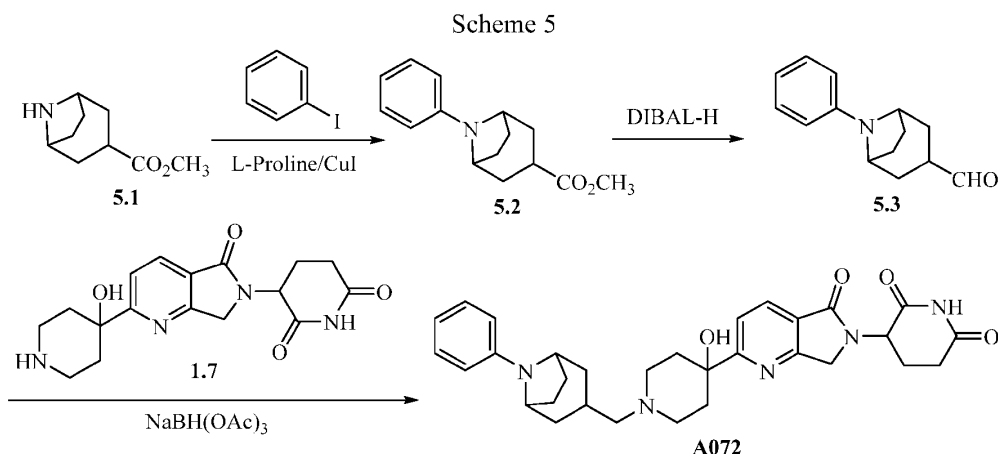
[0348] Preparation of 3-(2-(4-hydroxy-1-((1-(pyridin-3-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A071**. To a solution of compound **4.2** (60 mg, 315 μ mol) and 3-(2-(4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **1.7** as a HCl salt (80 mg, 210 μ mol) in DMF (2 mL) was added NaBH(OAc)₃ (134 mg, 630 μ mol). After stirring for 12 h, the reaction mixture was concentrated and purified by prep-HPLC (C18, ACN in water containing 0.05% TFA) to afford compound **A071** (57 mg) in 52% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.03 (s, 1H), 9.03 (s, 1H), 8.41 (s, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 3.6 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.85-7.75 (m, 1H), 7.65-7.53 (m, 1H), 5.98 (s, 1H), 5.20 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.57-4.29 (m, 2H), 3.92 (d, *J* = 12.0 Hz, 2H), 3.56-3.53 (m, 2H), 3.14-3.11 (m, 2H), 2.99-2.83 (m, 4H), 2.62-2.56 (m, 3H), 2.47-2.38 (m, 2H), 2.14-2.01 (m, 2H), 1.92-1.77 (m, 4H), 1.37-1.25 (m, 2H); MS (ESI) *m/z*: 519.4 [M+H]⁺.

EXAMPLE 5

Synthesis of 3-(2-(4-hydroxy-1-((8-phenyl-8-azabicyclo[3.2.1]octan-3-yl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A072**



[0349] Compound **A072** was prepared as shown in Scheme 5.



[0350] Preparation of methyl 8-phenyl-8-azabicyclo[3.2.1]octane-3-carboxylate **5.2**. To a solution of methyl 8-azabicyclo[3.2.1]octane-3-carboxylate **5.1** (400 mg, 2.36 mmol) and iodobenzene (964 mg, 4.73 mmol) in DMSO (4.00 mL) were added L-proline (108 mg, 945 μ mol), CuI (90 mg, 472 μ mol), and K_2CO_3 (653 mg, 4.73 mmol) under N_2 . After stirring at 80 $^{\circ}C$ for 12 h, the reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated, and purified by prep-TLC (SiO_2 , EtOAc/PE) to afford compound **5.2** (80 mg) in 13% yield. 1H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, J = 8.0 Hz, 2H), 6.78 (d, J = 8.0 Hz, 2H), 6.72 (t, J = 7.2 Hz, 1H), 4.29 (s, 2H), 3.60 (s, 3H), 2.97-2.88 (m, 1H), 2.14-2.11 (m, 2H), 2.05 (t, J = 12.6 Hz, 2H), 1.84-1.78 (m, 2H), 1.67-1.63 (m, 2H); MS (ESI) m/z : 246.0 $[M+H]^+$.

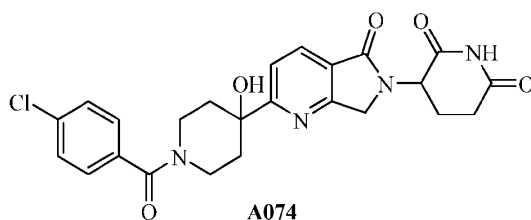
[0351] Preparation of 8-phenyl-8-azabicyclo[3.2.1]octane-3-carbaldehyde **5.3**. To a solution of compound **5.2** (75 mg, 291 μ mol) in toluene (1.5 mL) was added 1M DIBAL-H (291 μ L) at -60 $^{\circ}C$ under N_2 . After stirring at -60 $^{\circ}C$ for 2 h, the reaction mixture was dropwise added to MeOH (2 mL) and brine (8 mL) at -60 $^{\circ}C$. After warming up to room temperature, the reaction mixture was filtered and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated to afford compound **5.3** (40 mg), which was used directly in the next step without further purification. MS (ESI) m/z : 216.1 $[M+H]^+$.

[0352] Preparation of 3-(2-(4-hydroxy-1-((8-phenyl-8-azabicyclo[3.2.1]octan-3-yl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A072**. To a solution of

compound **5.3** (40 mg, 185 μ mol) and 3-(2-(4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]-pyridin-6-yl)piperidine-2,6-dione as a HCl salt (64 mg, 185 μ mol) in DMF (1 mL) was added NaBH(OAc)₃ (118 mg, 557 μ mol). After stirring for 12 h, the reaction mixture was filtered and purified by prep-HPLC (C18, ACN in water containing 10 mM NH₄HCO₃) to afford compound **A072** (28 mg) in 27% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.01 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.16-7.12 (m, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.57 (t, *J* = 7.2 Hz, 1H), 5.19-5.14 (m, 2H), 4.49 (d, *J* = 16.0 Hz, 1H), 4.34-4.29 (m, 1H), 4.22 (s, 2H), 2.96-2.87 (m, 1H), 2.62-2.59 (m, 3H), 2.46-2.38 (m, 1H), 2.30-2.13 (m, 5H), 2.04-1.94 (m, 5H), 1.80-1.77 (m, 2H), 1.50-1.42 (m, 4H), 1.36-1.31 (m, 2H); MS (ESI) *m/z*: 544.4 [M+H]⁺.

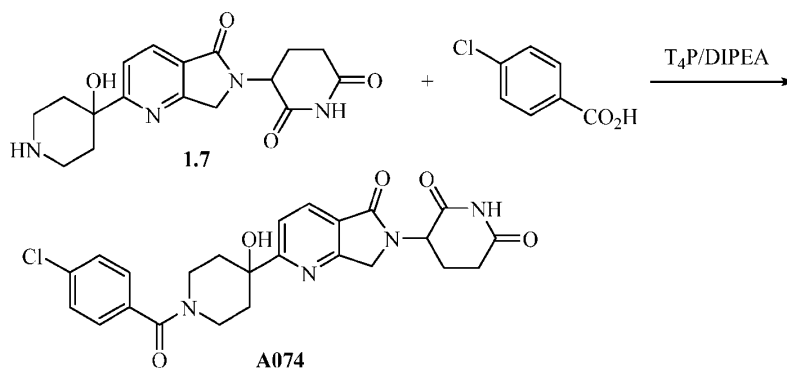
EXAMPLE 6

Synthesis of 3-(2-(1-(4-chlorobenzoyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A074**



[0353] Compound **A074** was prepared as shown in Scheme 6.

Scheme 6

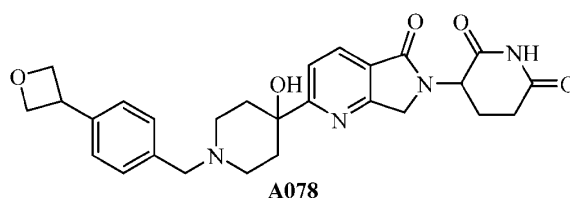


[0354] To a solution of 4-chlorobenzoic acid (41.1 mg, 262 μ mol) in DMF (1 mL) were added 3-(2-(4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **1.7** as a HCl salt (100 mg, 262 μ mol), DIPEA (135 mg, 1.05 mmol), and 50% T₄P (378 mg, 525 μ mol). After stirring for 30 min, the reaction mixture was diluted with DMF (0.5 mL) and purified by

prep-HPLC (C18, ACN in water containing 10 mM NH_4HCO_3) to afford compound **A074** (47 mg) in 37% yield. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.9 (s, 1H), 8.17 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.53-7.46 (m, 4H), 5.68 (s, 1H), 5.20-5.15 (m, 1H), 4.54-4.32 (m, 3H), 3.53-3.50 (m, 2H), 3.27-3.20 (m, 1H), 2.97-2.88 (m, 1H), 2.64-2.59 (m, 1H), 2.46-2.41 (m, 1H), 2.14-2.01 (m, 3H), 1.72-1.58 (m, 2H); MS (ESI) m/z : 483.2 $[\text{M}+\text{H}]^+$.

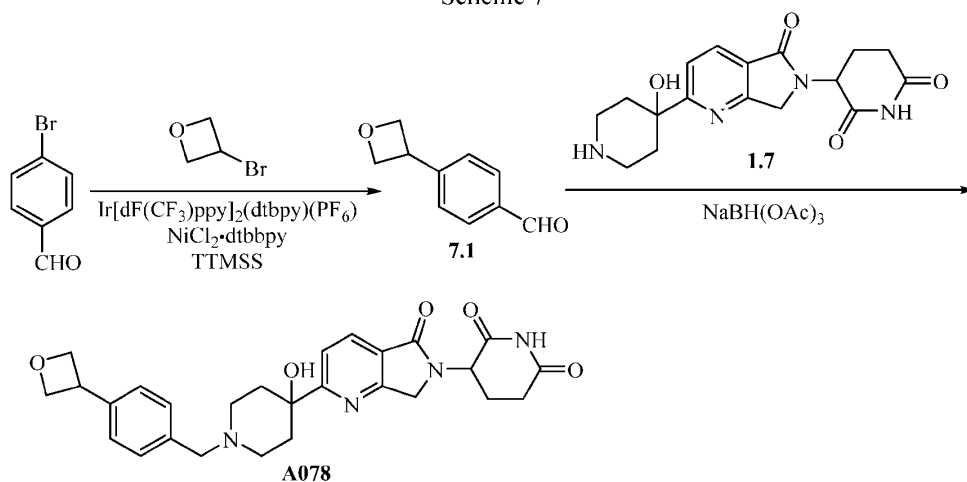
EXAMPLE 7

Synthesis of 3-(2-(4-hydroxy-1-((4-(oxetan-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo-[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A078**



[0355] Compound **A078** was prepared as shown in Scheme 7.

Scheme 7



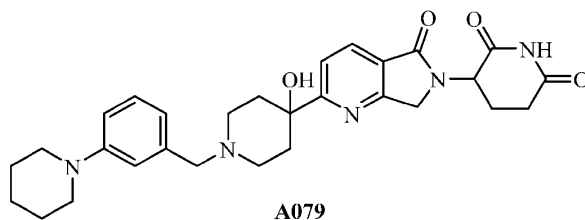
[0356] Preparation of 4-(oxetan-3-yl)benzaldehyde **7.1**. A mixture of 4-bromobenzaldehyde (500 mg, 2.70 mmol), 3-bromooxetane (481 mg, 3.51 mmol), $\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})(\text{PF}_6)_3$ (30.3 mg, 27 μmol), $\text{NiCl}_2\cdot\text{dtbbpy}$ (16.1 mg, 40.5 μmol), TTMSS (671 mg, 2.7 mmol), and Na_2CO_3 (572 mg, 5.40 mmol) in DME (10 mL) under N_2 was stirred and irradiated with a 10 W blue LED lamp (3 cm away) at room temperature for 14 h. The reaction mixture was then filtered, concentrated, and purified by prep-TLC (SiO_2 , EtOAc/PE) to afford compound **7.1** (200 mg) in

44% yield. ^1H NMR (400 MHz, DMSO- d_6) δ 10.00 (s, 1H), 7.92-7.90 (m, 2H), 7.63 (d, J = 8.0 Hz, 2H), 4.99-4.94 (m, 2H), 4.65-4.62 (m, 2H), 4.39-4.32 (m, 1H); MS (ESI) m/z : 163.1 $[\text{M}+\text{H}]^+$.

[0357] Preparation of 3-(2-(4-hydroxy-1-((4-(oxetan-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A078**. To a solution of compound **7.1** (50 mg, 295 μmol) in DMF (2 mL) were added 3-(2-(4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **1.7** as a HCl salt (112 mg, 295 μmol) and $\text{NaBH}(\text{OAc})_3$ (187 mg, 886 μmol). After stirring for 5 h, the reaction mixture was diluted with H_2O (0.5 mL) and purified by prep-HPLC (C18, ACN in water containing 0.225% FA) to afford compound **A078** (34 mg) in 23% yield. ^1H NMR (400 MHz, DMSO- d_6) δ 11.00 (s, 1H), 8.17-8.11 (m, 2H), 7.84 (d, J = 8.4 Hz, 1H), 7.37-7.33 (m, 4H), 5.37-5.20 (m, 1H), 5.18-5.12 (m, 1H), 4.94-4.91 (m, 2H), 4.61 (t, J = 6.4 Hz, 2H), 4.52-4.47 (m, 1H), 4.34-4.30 (m, 1H), 4.27-4.19 (m, 1H), 3.55 (s, 2H), 2.96-2.87 (m, 1H), 2.69-2.67 (m, 2H), 2.63-2.58 (m, 1H), 2.45-2.38 (m, 3H), 2.25-2.19 (m, 2H), 2.03-2.01 (m, 1H), 1.56-1.53 (m, 2H); MS (ESI) m/z : 491.2 $[\text{M}+\text{H}]^+$.

EXAMPLE 8

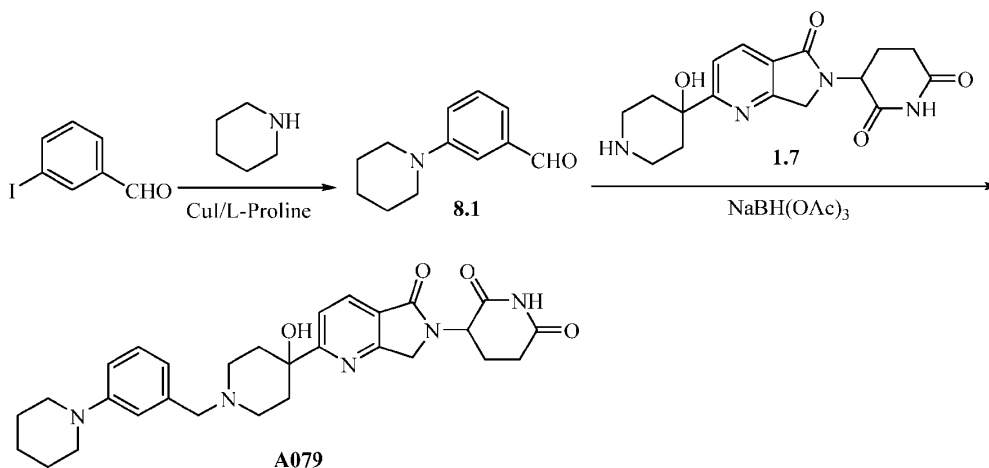
Synthesis of 3-(2-(4-hydroxy-1-((3-(1-piperidyl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A079**



[0358] Compound **A079** was prepared as shown in Scheme 8.

[0359] Preparation of 3-(1-piperidyl)benzaldehyde **8.1**. To a solution of 3-iodobenzaldehyde (500 mg, 2.16 mmol) and piperidine (550 mg, 6.47 mmol) in DMSO (10 mL) were added K_2CO_3 (1.19 g, 8.62 mmol), CuI (82 mg, 431 μmol), and L-proline (99.2 mg, 862 μmol) under N_2 . After stirring at 60 $^\circ\text{C}$ for 12 h under N_2 , the reaction mixture was poured into H_2O (60 mL) at 0-5 $^\circ\text{C}$ and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated, and purified by prep-TLC (SiO_2 , EtOAc/PE) to afford compound **8.1** (290 mg) in 64% yield. ^1H NMR (400 MHz, DMSO- d_6) δ 9.93 (s, 1H), 7.43-7.39 (m, 2H), 7.28-7.25 (m, 2H), 3.24-3.21 (m, 4H), 1.65-1.55 (m, 6H); MS (ESI) m/z : 190.1 $[\text{M}+\text{H}]^+$.

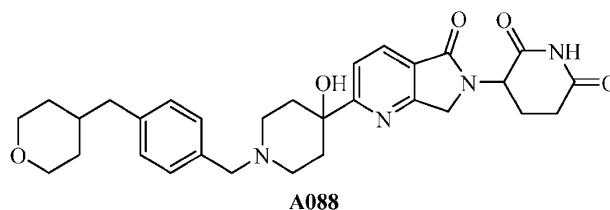
Scheme 8



[0360] Preparation of 3-(2-(4-hydroxy-1-((3-(1-piperidyl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A079**. To a solution of compound **8.1** (55.2 mg, 262 μmol) and 3-(2-(4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)-piperidine-2,6-dione **1.7** as a HCl salt (100 mg, 262 μmol) in DMF (1.00 mL) was added $\text{NaBH}(\text{OAc})_3$ (166 mg, 787 μmol). After stirring for 4 h, the reaction mixture was diluted with H_2O (0.50 mL) and purified by prep-HPLC (C18, ACN in water containing 0.225% FA) to afford compound **A079** (21 mg) in 14% yield. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.0 (s, 1H), 8.20 (s, 1H), 8.13 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.16-7.12 (m, 1H), 6.90 (s, 1H), 6.82-6.79 (m, 1H), 6.74 (d, $J = 8.0$ Hz, 1H), 5.18-5.14 (m, 1H), 4.50 (d, $J = 18.0$ Hz, 1H), 4.33 (d, $J = 18.0$ Hz, 1H), 3.53 (s, 2H), 3.12-3.10 (m, 4H), 2.96-2.87 (m, 1H), 2.72 (d, $J = 10.4$ Hz, 2H), 2.63-2.58 (m, 1H), 2.52-2.50 (m, 1H), 2.46-2.37 (m, 2H), 2.26-2.20 (m, 2H), 2.05-1.99 (m, 1H), 1.64-1.52 (s, 8H); MS (ESI) m/z : 518.1 $[\text{M}+\text{H}]^+$.

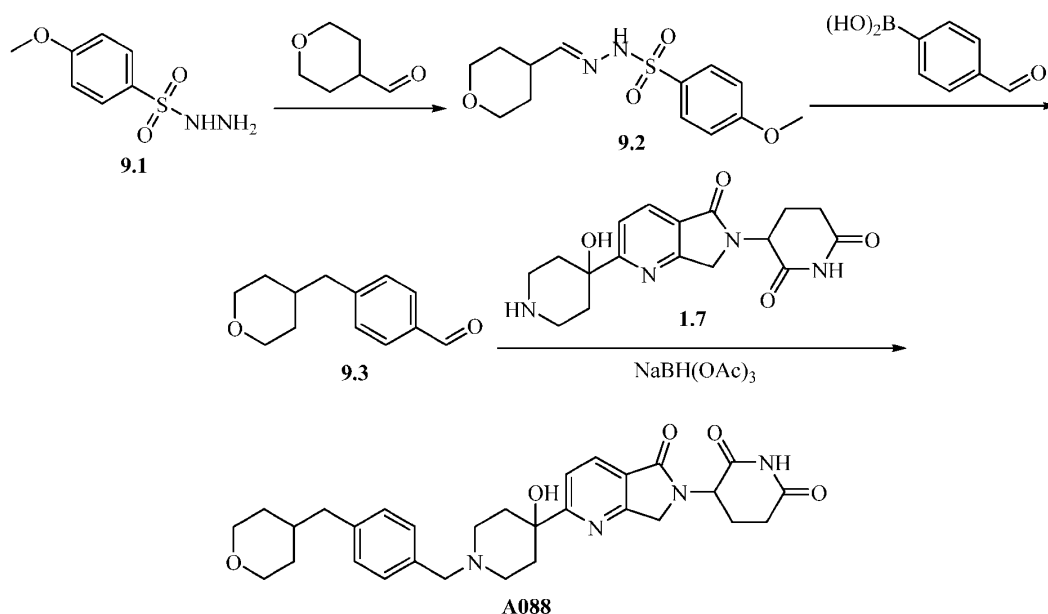
EXAMPLE 9

Synthesis of 3-(2-(4-hydroxy-1-((4-(tetrahydropyran-4-ylmethyl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A088**



[0361] Compound **A088** was prepared as shown in Scheme 9.

Scheme 9



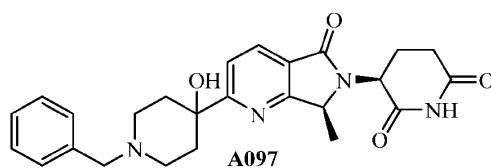
[0362] Preparation of 4-methoxy-*N*-((*E*)-tetrahydropyran-4-ylmethyleneamino)benzenesulfonamide **9.2**. To a solution of tetrahydropyran-4-carbaldehyde (500 mg, 4.38 mmol) in MeOH (5.00 mL) was portion wise added 4-methoxybenzenesulfonylhydrazide **9.1** (885 mg, 4.38 mmol) under N₂. After stirring for 1.5 h, the reaction mixture was concentrated to afford compound **9.2** (400 mg), which was used directly in the next step without further purification. MS (ESI) *m/z*: 299.1 [M+H]⁺.

[0363] Preparation of 4-(tetrahydropyran-4-ylmethyl)benzaldehyde **9.3**. To a solution of compound **9.2** (200 mg, 670 μmol) and (4-formylphenyl)boronic acid (201 mg, 1.34 mmol) in dioxane (4.00 mL) was added K₂CO₃ (138 mg, 1.01 mmol). After stirring at 100 °C for 3 h, the residue mixture was poured into H₂O (20 mL) and extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with brine (3 x 60 mL), dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by prep-TLC (SiO₂, EtOAc/PE) to afford compound **9.3** (60 mg) in 39% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.95 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 3.81-3.78 (m, 2H), 3.24-3.18 (m, 2H), 2.61 (d, *J* = 7.4 Hz, 2H), 1.83-1.72 (m, 1H), 1.46-1.42 (m, 2H), 1.25-1.16 (m, 2H); MS (ESI) *m/z*: 205.2 [M+H]⁺.

[0364] Preparation of 3-(2-(4-hydroxy-1-((4-(tetrahydropyran-4-ylmethyl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A088**. To a solution of 3-(2-(4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **1.7** as a HCl salt (98 mg, 257 μ mol) and compound **9.3** (59 mg, 257 μ mol) in DMF (1.00 mL) was added NaBH(OAc)₃ (163 mg, 772 μ mol). After stirring for 12 h, the reaction mixture was filtered and purified by prep-HPLC (C18, ACN in water containing 0.225% FA) to afford compound **A088** (34 mg) in 23% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.19 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.28-5.22 (m, 1H), 5.18-5.14 (m, 1H), 4.50 (d, *J* = 17.8 Hz, 1H), 4.34-4.30 (m, 1H), 3.81-3.78 (m, 2H), 3.48 (s, 2H), 3.22-3.19 (m, 4H), 2.95-2.84 (m, 1H), 2.68-2.61 (m, 3H), 2.45-2.37 (m, 3H), 2.23-2.17 (m, 2H), 2.08-2.01 (m, 1H), 1.75-1.68 (m, 1H), 1.55-1.52 (m, 2H), 1.48-1.45 (m, 2H), 1.23-1.13 (m, 2H); MS (ESI) *m/z*: 533.3 [M+H]⁺.

EXAMPLE 10

Synthesis of (3*S*)-3-((7*S*)-2-(1-benzyl-4-hydroxy-4-piperidyl)-7-methyl-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A097**



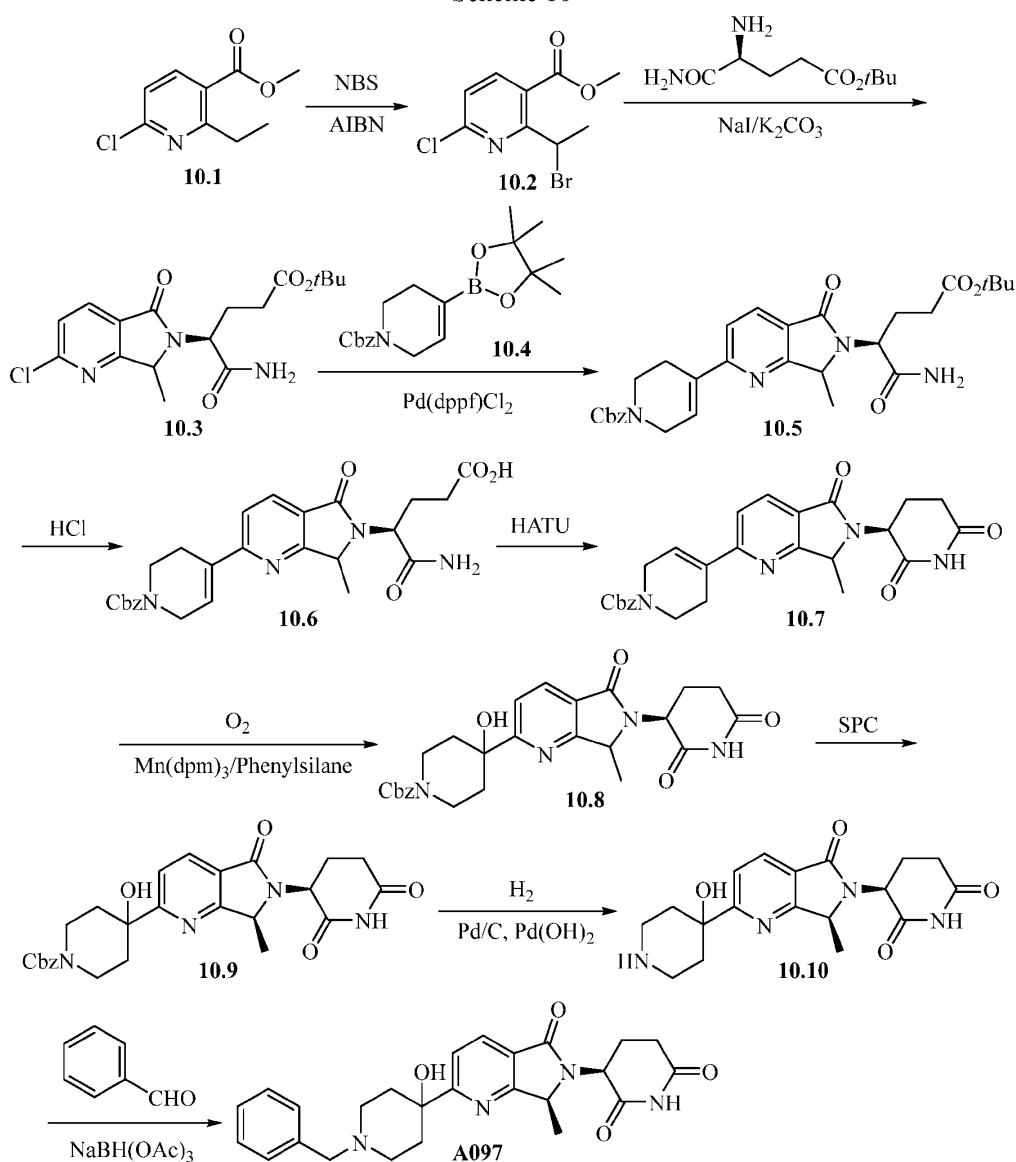
[0365] Compound **A097** was prepared as shown in Scheme 10.

[0366] Preparation of methyl 2-(1-bromoethyl)-6-chloronicotinate **10.2**. To a solution of methyl 6-chloro-2-ethylnicotinate **10.1** (72.7 g, 338 mmol) in ACN (800 mL) were added NBS (102 g, 575 mmol) and AIBN (22.2 g, 135 mmol). After stirring at 80 °C for 16 h, the reaction mixture was cooled to room temperature, concentrated, and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **10.2** (170 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.09-8.07 (m, 1H), 7.25-7.23 (m, 1H), 6.23-6.18 (m, 1H), 3.88 (s, 3H), 2.01-1.99 (m, 3H).

[0367] Preparation of *tert*-butyl (4*S*)-5-amino-4-(2-chloro-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-5-oxopentanoate **10.3**. To a solution of compound **10.2** (100 g, 359 mmol) in ACN (1 L) were added K₂CO₃ (99.2 g, 718 mmol), *tert*-butyl (*S*)-4,5-diamino-5-oxopentanoate (111 g, 466 mmol) and NaI (10.7 g, 71.8 mmol). After stirring at 80 °C for 16 h, the reaction mixture was poured into H₂O (2 L) and extracted with EtOAc (2 x 2 L). The

combined organic layers were washed with brine (2 x 1 L), dried over anhydrous Na_2SO_4 , filtered, concentrated, and triturated with EtOAc/PE (500 mL) for 30 min to afford compound **10.3** (70 g) in 51% yield. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.14-8.12 (m, 1H), 7.64-7.62 (m, 1H), 7.46-7.18 (m, 2H), 4.71-7.66 (m, 1H), 4.48-4.42 (m, 1H), 2.28-2.15 (m, 4H), 1.51-1.42 (m, 3H), 1.36 (s, 9H); MS (ESI) m/z : 368.0 $[\text{M}+\text{H}]^+$.

Scheme 10



[0368] Preparation of benzyl 4-(6-((*S*)-1-amino-5-(*tert*-butoxy)-1,5-dioxopentan-2-yl)-7-methyl-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **10.5**. To a solution of compound **10.3** (21.5 g, 57.9 mmol) and benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate **10.4** (35.7 g, 104 mmol) in dioxane (200 mL) and H₂O (200 mL) were added K₃PO₄ (36.8 g, 173 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (5.2 g, 6.37 mmol) under N₂. After stirring at 50 °C for 12 h under N₂, the reaction mixture was poured into H₂O (500 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated, and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **10.5** (19.2 g) in 56% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.44-7.39 (m, 5H), 7.29 (s, 1H), 7.20 (s, 1H), 6.94 (s, 1H), 5.18 (s, 2H), 4.72-4.51 (m, 2H), 4.24 (s, 2H), 3.70 (s, 2H), 2.72-2.69 (m, 2H), 2.40-2.19 (m, 4H), 1.58 (d, *J* = 6.8 Hz, 1H), 1.50 (d, *J* = 6.4 Hz, 2H), 1.42 (m, 9H); MS (ESI) *m/z*: 549.4 [M+H]⁺.

[0369] Preparation of (4*S*)-5-amino-4-(2-(1-((benzyloxy)carbonyl)-1,2,3,6-tetrahydropyridin-4-yl)-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-5-oxopentanoic acid **10.6**. To solution of 12M HCl (21.1 mL) in ACN (150 mL) was added compound **10.5** (15 g, 25.4 mmol) in ACN (150 mL) at 0-5 °C. After stirring for 2 h, the reaction mixture was poured into H₂O (400 mL) at 0-5 °C and extracted with EtOAc/THF (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated to afford compound **10.6** (13 g), which was used directly in the next step without further purification. MS (ESI) *m/z*: 493.1 [M+H]⁺.

[0370] Preparation of benzyl 4-(6-((3*S*)-2,6-dioxo-3-piperidyl)-7-methyl-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate **10.7**. To a solution of compound **10.6** as a HCl salt (12.9 g, 19.8 mmol) in ACN (120 mL) were added DIPEA (7.71 g, 59.6 mmol) and HATU (15.1 g, 39.7 mmol). After stirring for 2 h, the reaction mixture was poured into H₂O (400 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na₂SO₄, concentrated, and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **10.7** (9.4 g). MS (ESI) *m/z*: 475.2 [M+H]⁺.

[0371] Preparation of benzyl 4-(6-((*S*)-2,6-dioxopiperidin-3-yl)-7-methyl-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidine-1-carboxylate **10.8**. To a solution of

compound **10.7** (2 g, 4.21 mmol) in DCM (20 mL), IPA (20 mL), and DMF (20 mL) were added Mn(dpm)₃ (509 mg, 842 μ mol) and phenylsilane (912 mg, 8.43 mmol) at 0 °C under O₂. After stirring for 1.5 h, the reaction mixture was poured into H₂O (50.0 mL) at 0-5 °C and extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated, triturated with MTBE/DCM (30 mL) for 10 min, and purified by prep-HPLC (C18, ACN in water containing 0.225% FA) to afford compound **10.8** (860 mg) in 41% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.9 (s, 1H), 8.11 (d, *J* = 6.4 Hz, 1H), 7.84 (d, *J* = 6.4 Hz, 1H), 7.38-7.32 (m, 5H), 5.75 (s, 3H), 5.59 (s, 1H), 5.11 (s, 2H), 4.84-4.63 (m, 2H), 3.98-3.95 (m, 2H), 2.85-2.58 (m, 3H), 2.13-2.03 (m, 3H), 1.60-4.57 (m, 2H), 1.47-1.42 (m, 3H); MS (ESI) *m/z*: 493.2 [M+H]⁺.

[0372] Preparation of benzyl 4-((*S*)-6-((*S*)-2,6-dioxopiperidin-3-yl)-7-methyl-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidine-1-carboxylate **10.9**. Compound **10.8** (400 mg, 806 μ mol) was resolved by SFC isocratically using a DAICEL CHIRALPAK AD chiral column to afford compound **10.9** (200 mg) in 50% yield. MS (ESI) *m/z*: 493.1 [M+H]⁺.

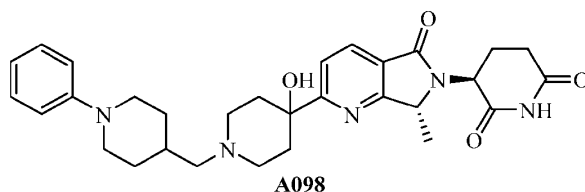
[0373] Preparation of (*S*)-3-((*S*)-2-(4-hydroxypiperidin-4-yl)-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **10.10**. To a solution of compound **10.9** (190 mg, 383 μ mol) in THF (6 mL) and TFE (2 mL) were added 10% Pd/C (100 mg) and 20% Pd(OH)₂ (100 mg). After stirring for 12 h under H₂ (15 psi), the reaction mixture was filtered through celite and the filter cake was washed with EtOH (3 x 150 mL). The filtrate was concentrated and purified by prep-HPLC (C18, ACN in water containing 10 mM NH₄HCO₃) to afford compound **10.10** (50 mg) in 33% yield. MS (ESI) *m/z*: 359.0 [M+H]⁺.

[0374] Preparation of (*S*)-3-((*S*)-2-(1-benzyl-4-hydroxypiperidin-4-yl)-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A097**. To a solution of compound **10.10** (50 mg, 127 μ mol) and benzaldehyde (13.5 mg, 127 μ mol) in DMF (1 mL) was added NaBH(OAc)₃ (81.3 mg, 383 μ mol). After stirring for 12 h, the reaction mixture was diluted with DMF (0.5 mL) and purified by prep-HPLC (C18, ACN in water containing 10 mM NH₄HCO₃), prep-HPLC (C18, ACN in water containing 0.225% FA) and prep-HPLC (DAICEL CHIRALPAK IF) to afford compound **A097** (19 mg) in 32% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.9 (s, 1H), 8.17 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.34-7.33 (m, 4H), 7.27-7.23 (m, 1H), 5.42-5.16 (m, 1H), 4.84-4.79 (m, 1H), 4.68-4.63 (m, 1H), 3.55

(s, 2H), 2.85-2.80 (m, 1H), 2.69-2.58 (m, 4H), 2.45-2.42 (m, 2H), 2.30-2.17 (m, 2H), 2.04-1.99 (m, 1H), 1.58-1.53 (m, 2H), 1.45 (d, $J = 6.8$ Hz, 3H); MS (ESI) m/z : 449.2 $[M+H]^+$.

EXAMPLE 11

Synthesis of (*S*)-3-((*R*)-2-(4-hydroxy-1-((1-phenylpiperidin-4-yl)methyl)piperidin-4-yl)-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A098**



[0375] Compound **A098** was prepared as shown in Scheme 11.

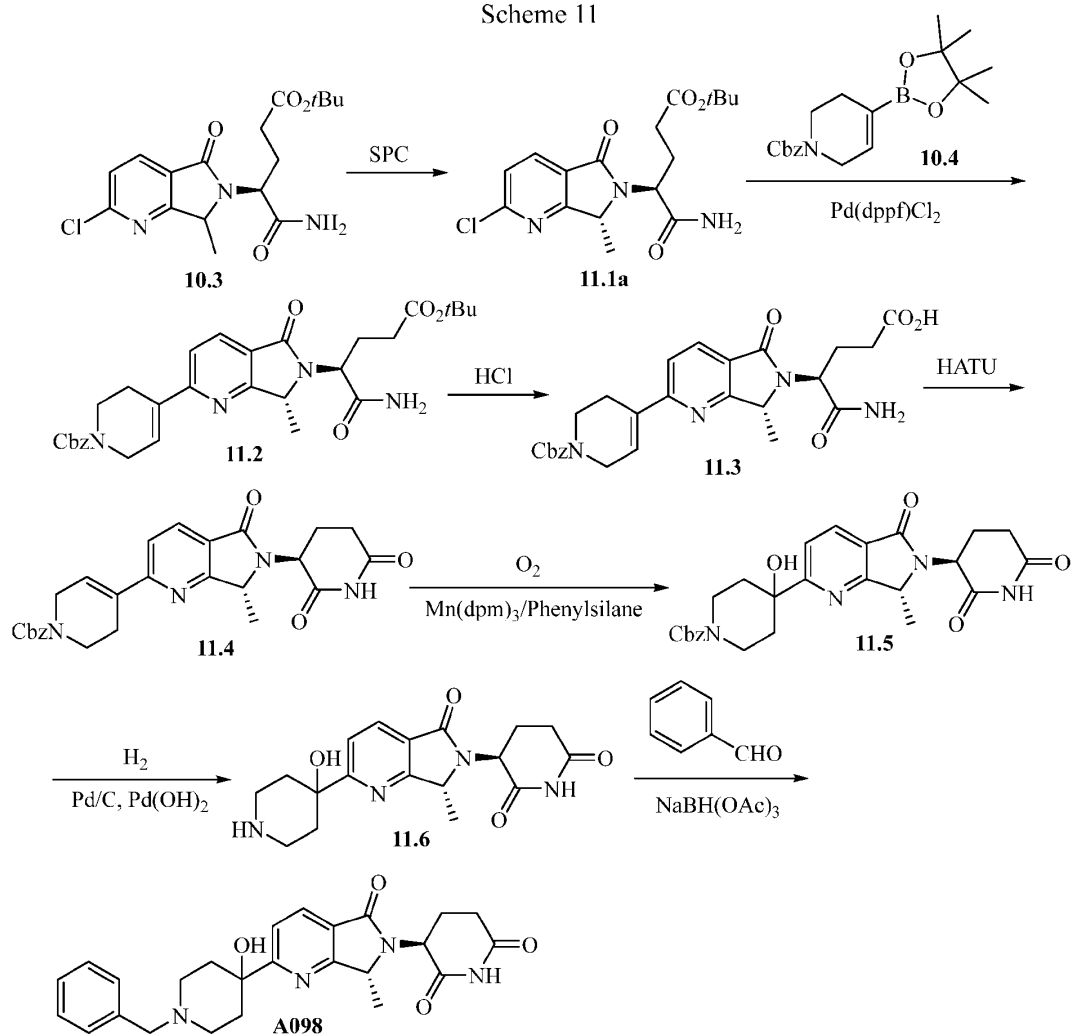
[0376] Preparation of *tert*-butyl (*S*)-5-amino-4-((*R*)-2-chloro-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-5-oxopentanoate **11.1a** and *tert*-butyl (*S*)-5-amino-4-((*S*)-2-chloro-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-5-oxopentanoate **11.1b**. *Tert*-butyl (4*S*)-5-amino-4-(2-chloro-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-5-oxopentanoate **10.3** was resolved by SFC isocratically using a DAICEL CHIRALPAK AD chiral column to afford compounds **11.1a** and **11.1b**. Compound **11.1a**: ^1H NMR (400 MHz, DMSO- d_6) δ 8.14-8.12 (m, 1H), 7.64-7.62 (m, 1H), 7.45-7.24 (m, 2H), 4.73-7.69 (m, 1H), 4.48-4.45 (m, 1H), 2.26-2.18 (m, 4H), 1.51-1.49 (m, 3H), 1.36 (s, 9H); MS (ESI) m/z : 390.1 $[M+Na]^+$.

Compound **11.1b**: ^1H NMR (400 MHz, DMSO- d_6) δ 8.14-8.12 (m, 1H), 7.64-7.62 (m, 1H), 7.46-7.18 (m, 2H), 4.71-4.66 (m, 1H), 4.47-4.42 (m, 1H), 2.35-2.15 (m, 4H), 1.51-1.42 (m, 3H), 1.35 (s, 9H); MS (ESI) m/z : 390.1 $[M+Na]^+$.

[0377] Preparation of (*S*)-3-((*R*)-2-(4-hydroxy-1-((1-phenylpiperidin-4-yl)methyl)piperidin-4-yl)-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A098**.

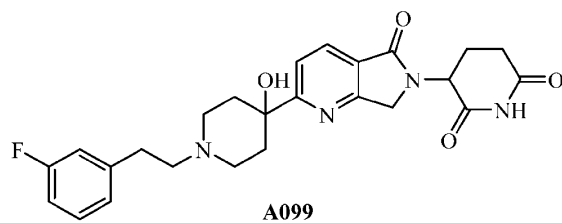
Compound **A098** was prepared from compound **11.1a** similarly as described in Example 10. ^1H NMR (400 MHz, DMSO- d_6) δ 10.9 (s, 1H), 8.17 (s, 1H), 8.09-8.07 (m, 1H), 7.84-7.82 (m, 1H), 7.20-7.16 (m, 2H), 6.93-6.91 (m, 2H), 6.74-6.71 (m, 1H), 5.59-5.23 (m, 1H), 4.85-4.80 (m, 1H), 4.71-4.62 (m, 1H), 3.69-3.66 (m, 2H), 2.89-2.74 (m, 3H), 2.69-2.59 (m, 4H), 2.46-2.41 (m, 2H), 2.32-2.19 (m, 4H), 2.07-2.00 (m, 1H), 1.83-1.69 (m, 3H), 1.58-1.55 (m, 2H), 1.46-1.44 (m, 3H), 1.27-1.17 (m, 2H); MS (ESI) m/z : 532.4 $[M+H]^+$.

Scheme 11



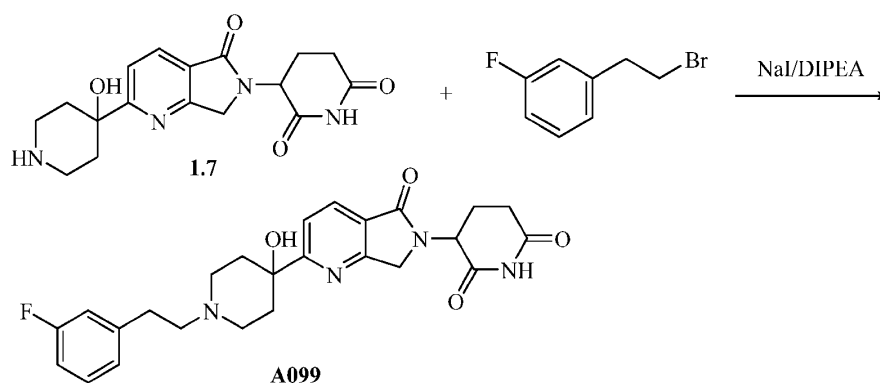
EXAMPLE 12

Synthesis of 3-(2-(1-(2-(3-fluorophenyl)ethyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A099**



[0378] Compound **A099** was prepared as shown in Scheme 12.

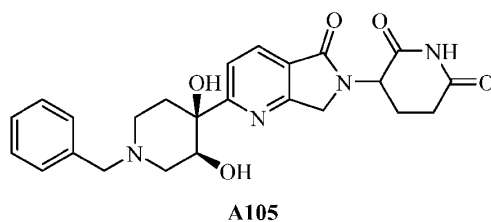
Scheme 12



[0379] To a solution of 3-(2-(4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-piperidine-2,6-dione **1.7** as a HCl salt (100 mg, 262 μ mol) in DMF (2.00 mL) were added 1-(2-bromoethyl)-3-fluorobenzene (53.3 mg, 262 μ mol), DIPEA (203 mg, 1.58 mmol), and NaI (196 mg, 1.31 mmol). After stirring at 50 °C for 6 h, the reaction mixture was filtered and purified by prep-HPLC (C18, ACN in water containing 10 mM NH_4HCO_3) to afford compound **A099** (18.5 mg) in 15% yield. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.01 (s, 1H), 8.18 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.34-7.29 (m, 1H), 7.11-7.08 (m, 2H), 7.03-6.98 (m, 1H), 5.30 (s, 1H), 5.19-5.14 (m, 1H), 4.52-4.46 (m, 1H), 4.34-4.30 (m, 1H), 2.96-2.87 (m, 1H), 2.82-2.78 (m, 4H), 2.63-2.59 (m, 3H), 2.45-2.37 (m, 3H), 2.23-2.17 (m, 2H), 2.05-1.99 (m, 1H), 1.59-1.55 (m, 2H); MS (ESI) m/z : 467.3 $[\text{M}+\text{H}]^+$.

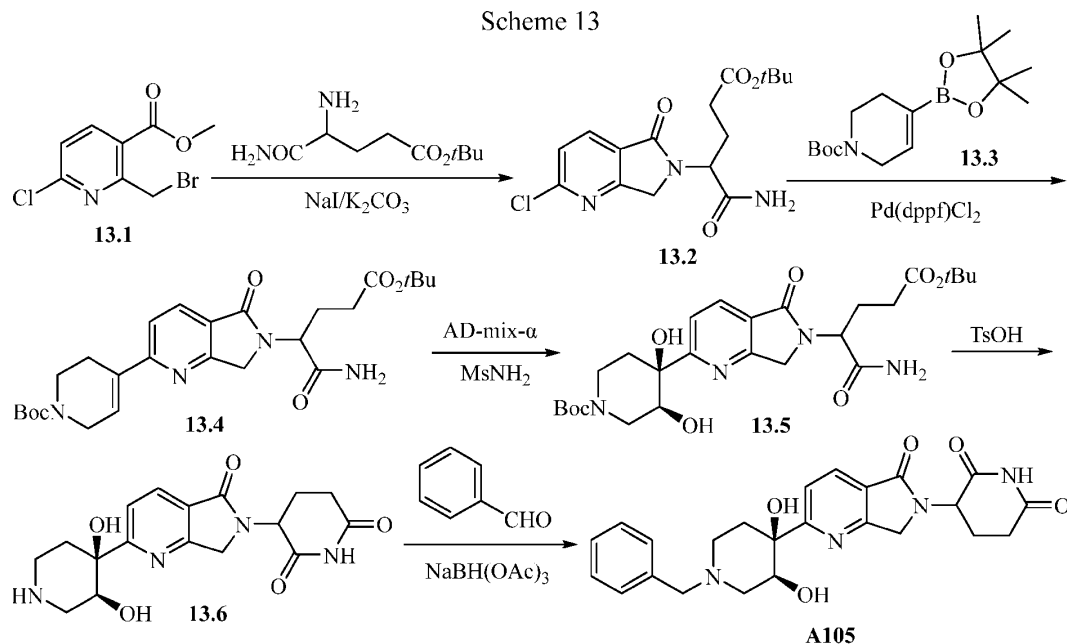
EXAMPLE 13

Synthesis of 3-(2-((3*S*,4*S*)-1-benzyl-3,4-dihydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A105**



[0380] Compound **A105** was prepared as shown in Scheme 13.

Scheme 13



[0381] Preparation of *tert*-butyl 5-amino-4-(2-chloro-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-5-oxopentanoate **13.2**. To a solution of methyl 2-(bromomethyl)-6-chloropyridine-3-carboxylate **13.1** (23 g, 75.3 mmol) in ACN (400 mL) were added *tert*-butyl 4,5-diamino-5-oxopentanoate as a HCl salt (26.9 g, 112 mmol), NaI (2.26 g, 15 mmol), and K₂CO₃ (20.8 g, 150 mmol). After stirring at 80 °C for 12 h, the reaction mixture was poured into H₂O (200 mL) and extracted with EtOAc (100 mL). The organic layer was concentrated to afford compound **13.2** (17 g) in 64% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (d, *J* = 8.0 Hz, 1H), 7.64-7.59 (m, 2H), 7.24 (s, 1H), 4.76-4.73 (m, 1H), 4.61-4.51 (m, 2H), 2.25-2.15 (m, 3H), 2.02-1.97 (m, 1H), 1.32 (s, 9H); MS (ESI) *m/z*: 376.1 [M+Na]⁺.

[0382] Preparation of *tert*-butyl 4-(6-(4-*tert*-butoxy-1-carbamoyl-4-oxo-butyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate **13.4**. To a solution of compound **13.2** in dioxane (170 mL) and H₂O (30 mL) were added *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylate **13.3** (22.2 g, 72 mmol), K₃PO₄ (15.3 g, 72 mmol), and Pd(dppf)Cl₂·CH₂Cl₂ (3.92 g, 4.8 mmol). After stirring at 50 °C for 12 h under N₂, the reaction mixture was poured into H₂O (200 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound

13.4 (22.4 g) in 87% yield. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.05 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 7.21 (s, 1H), 6.85 (s, 1H), 4.77-4.74 (m, 1H), 4.58-4.47 (m, 2H), 4.08 (s, 2H), 3.56-3.54 (m, 2H), 2.60 (s, 2H), 2.23-2.16 (m, 3H), 2.07-1.98 (m, 1H), 1.42 (s, 9H), 1.31 (s, 9H); MS (ESI) m/z : 501.3 $[\text{M}+\text{H}]^+$.

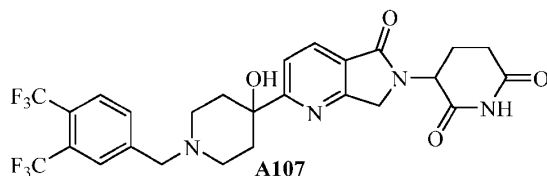
[0383] Preparation of *tert*-butyl (3*S*,4*S*)-4-(6-(4-*tert*-butoxy-1-carbamoyl-4-oxobutyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-3,4-dihydroxy-piperidine-1-carboxylate **13.5**. To a solution of AD-mix- α (3 g) and MsNH_2 (267 mg, 2.81 mmol) in *t*BuOH (5 mL) and H_2O (5 mL) at 0 °C under N_2 was added compound **13.4** (500 mg, 937 μmol). After stirring for 12 h, the reaction mixture was poured into H_2O (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, concentrated, and purified by column chromatography (SiO_2 , EtOAc/PE) and prep-HPLC (C18, ACN in water containing 0.225% FA) to afford compound **13.5** (400 mg) in 19% yield. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.07 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.20 (s, 1H), 5.32 (s, 1H), 4.77-4.73 (m, 2H), 4.59-4.45 (m, 2H), 3.95-3.90 (m, 3H), 3.02-2.87 (m, 2H), 2.21-2.15 (m, 3H), 2.07-1.98 (m, 2H), 1.58-1.52 (m, 1H), 1.42 (m, 9H), 1.33 (s, 9H); MS (ESI) m/z : 535.4 $[\text{M}+\text{H}]^+$.

[0384] Preparation of 3-(2-((3*S*,4*S*)-3,4-dihydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **13.6**. To a solution of compound **13.5** (350 mg, 631 μmol) in ACN (3 mL) was added TsOH (271 mg, 1.58 mmol). After stirring at 80 °C for 24 h, the reaction mixture was concentrated to afford compound **13.6** (200 mg), which was used directly in the next step without further purification. MS (ESI) m/z : 361.1 $[\text{M}+\text{H}]^+$.

[0385] Preparation of 3-(2-((3*S*,4*S*)-1-benzyl-3,4-dihydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A105**. To a solution of compound **13.6** (200 mg, 554 μmol) in DMF (2 mL) were added benzaldehyde (58.9 mg, 554 μmol) and $\text{NaBH}(\text{OAc})_3$ (352 mg, 1.66 mmol). After stirring for 12 h, the reaction mixture was diluted with H_2O (0.50 mL) and purified by prep-HPLC (C18, ACN in water containing 10 mM NH_4HCO_3) to afford compound **A105** (19 mg) in 7% yield. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.04-10.97 (m, 1H), 8.22 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.34-7.31 (m, 4H), 7.27-7.24 (m, 1H), 5.20-5.13 (m, 1H), 5.03-5.00 (m, 1H), 4.56-4.46 (m, 2H), 4.37-4.29 (m, 1H), 4.08-4.05 (m, 1H), 3.56-3.55 (m, 1H), 3.49 (s, 1H), 2.97-2.87 (m, 1H), 2.69-2.62 (m, 2H), 2.59-2.58 (m, 1H), 2.46-2.32 (m, 2H), 2.24-2.16 (m, 2H), 2.05-1.99 (m, 1H), 1.56-1.51 (m, 1H); MS (ESI) m/z : 451.1 $[\text{M}+\text{H}]^+$.

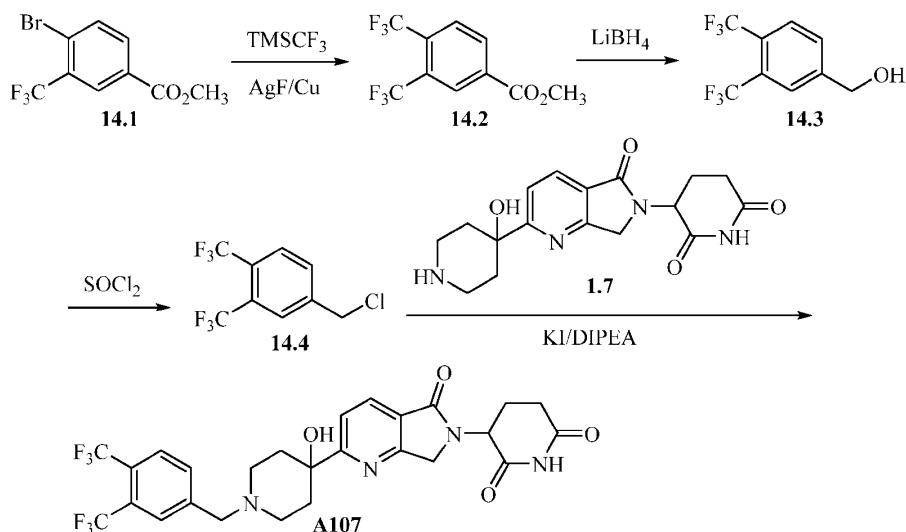
EXAMPLE 14

Synthesis of 3-(2-(1-((3,4-bis(trifluoromethyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A107**



[0386] Compound **A107** was prepared as shown in Scheme 14.

Scheme 14



[0387] Preparation of methyl 3,4-bis(trifluoromethyl)benzoate **14.2**. To a solution of AgF (5 g, 39.3 mmol) in DMF (100 mL) were added sequentially with stirring TMSCF₃ (6.68 g, 47 mmol), Cu (3.94 g, 62 mmol), and methyl 4-bromo-3-(trifluoromethyl)benzoate **14.1** (5 g, 17.6 mmol). After stirring at 100 °C for 12 h under N₂, the reaction mixture was filtered through celite, diluted with H₂O (300 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **14.2** (3.2 g) in 65% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.51 (s, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 4.00 (s, 3H).

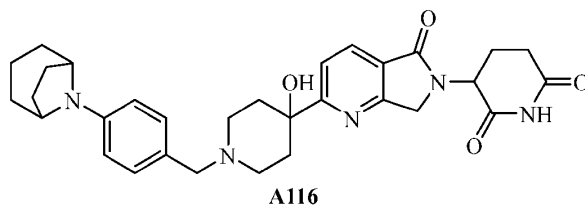
[0388] Preparation of (3,4-bis(trifluoromethyl)phenyl)methanol **14.3**. To a solution of compound **14.2** (3.2 g, 11.4 mmol) in THF (60 mL) was slowly added 2M LiBH₄ (17.1 mL) at 0-10 °C under N₂. After stirring at 70 °C for 12 h, the reaction mixture was allowed to cool to room temperature, neutralized with 1N HCl (50 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layers was washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to afford compound **14.3** (2.8 g) in 96% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.86-7.84 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 4.85 (s, 2H), 1.64-1.61 (m, 1H).

[0389] Preparation of 4-(chloromethyl)-1,2-bis(trifluoromethyl)benzene **14.4**. To a solution of compound **14.3** (300 mg, 1.23 mmol) in DCE (20 mL) was added DMF (0.1 mL) and SOCl₂ (730 mg, 6.14 mmol). After stirring at 50 °C for 1 h, the reaction mixture was concentrated to afford compound **14.4** (300 mg), which was used directly in the next step without further purification.

[0390] Preparation of 3-(2-(1-((3,4-bis(trifluoromethyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A107**. To a solution of compound **14.4** (152 mg, 580 μmol) in DMF (2 mL) were added 3-(2-(4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **1.7** as a HCl salt (100 mg, 290 μmol), KI (241 mg, 1.45 mmol), and DIPEA (225 mg, 1.74 mmol). After stirring at 50 °C for 2 h, the reaction mixture was filtered and purified by prep-HPLC (C18, ACN in water containing 10 mM NH₄HCO₃) to afford compound **A107** (42.6 mg) in 25% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.00 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.03-7.98 (m, 2H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 5.32 (s, 1H), 5.19-5.14 (m, 1H), 4.53-4.49 (m, 1H), 4.35-4.31 (m, 1H), 3.71 (s, 2H), 2.97-2.87 (m, 1H), 2.66-2.59 (m, 4H), 2.47-2.37 (m, 2H), 2.28-2.21 (m, 2H), 2.04-2.01 (m, 1H), 1.58-1.54 (m, 2H); MS (ESI) *m/z*: 571.3 [M+H]⁺.

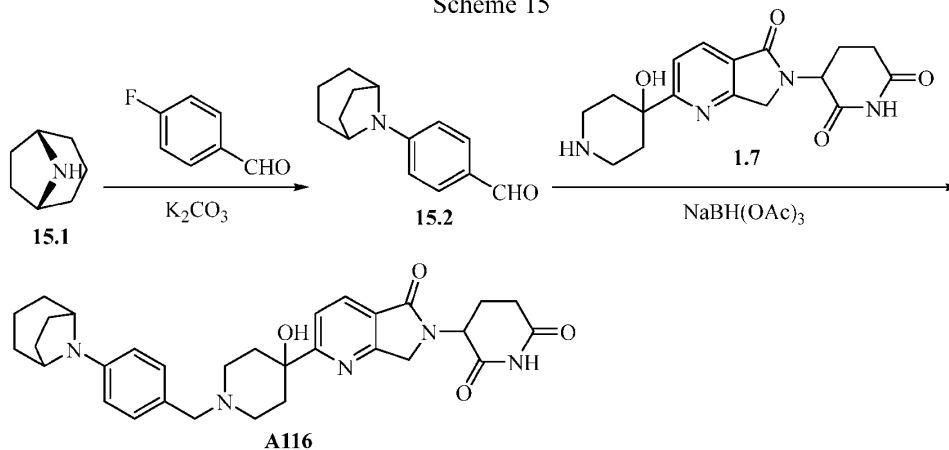
EXAMPLE 15

Synthesis of 3-(2-(1-(4-((1*R*,5*S*)-8-azabicyclo[3.2.1]octan-8-yl)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A116**



[0391] Compound **A116** was prepared as shown in Scheme 15.

Scheme 15



[0392] Preparation of 4-(8-azabicyclo[3.2.1]octan-8-yl)benzaldehyde **15.2**. To a solution of 8-azabicyclo[3.2.1]octane **15.1** as a HCl salt (237 mg, 1.61 mmol) in DMF (2 mL) were added 4-fluorobenzaldehyde (200 mg, 1.61 mmol) and K_2CO_3 (1.11 g, 8.06 mmol). After stirring at 90 °C for 12 h, the reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, concentrated, and purified by prep-TLC (SiO_2 , PE/EtOAc) to afford compound **15.2** (120 mg) in 34% yield.

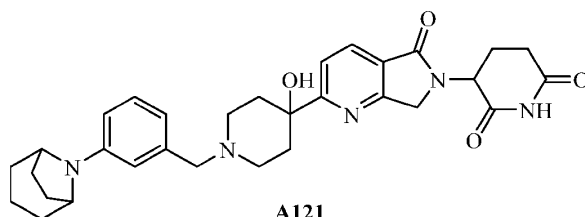
1H NMR (400 MHz, $DMSO-d_6$) δ 9.63 (s, 1H), 7.67 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 4.37 (s, 2H), 2.01-1.98 (m, 2H), 1.90-1.81 (m, 3H), 1.72-1.64 (m, 2H), 1.46-1.33 (m, 3H); MS (ESI) m/z : 216.0 $[M+H]^+$.

[0393] Preparation of 3-(2-(1-(4-((1R,5S)-8-azabicyclo[3.2.1]octan-8-yl)benzyl)-4-hydroxy-piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A116**. To a solution of compound **15.2** (46.5 mg, 210 μ mol) in DMF (1.00 mL) were added 3-(2-(4-hydroxy-4-piperidyl)-5-oxo-5,7-dihydro-6H-pyrrolo(3,4-b)pyridin-6-yl)piperidine-2,6-dione **1.7** as a HCl salt (80 mg, 210 μ mol) and $NaBH(OAc)_3$ (133 mg, 630 μ mol). After stirring for 12 h and 50 °C for 2 h, the reaction mixture was diluted with H_2O (0.5 mL) and purified by prep-HPLC (C18, ACN in water containing 0.225% FA) to afford compound **A116** (56 mg) in 47% yield. 1H NMR (400 MHz, $DMSO-d_6$) δ 11.01 (s, 1H), 8.20 (s, 1H), 8.13 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 1H), 7.12 (d, $J = 8.4$ Hz, 2H), 6.71 (d, $J = 8.4$ Hz, 2H), 5.41-5.27 (m, 1H), 5.19-5.14 (m, 1H), 4.51-4.47 (m, 1H), 4.34-4.29 (m, 1H), 4.16 (s, 2H), 3.45 (m, 2H), 2.96-2.87 (m, 1H), 2.73-2.70 (m,

2H), 2.62-2.58 (m, 1H), 2.45-2.37 (m, 3H), 2.25-2.18 (m, 2H), 2.04-1.94 (m, 3H), 1.84-1.72 (m, 5H) 1.58-1.54 (m, 2H), 1.40-1.37 (m, 1H), 1.23-1.20 (m, 2H); MS (ESI) m/z : 544.3 $[M+H]^+$.

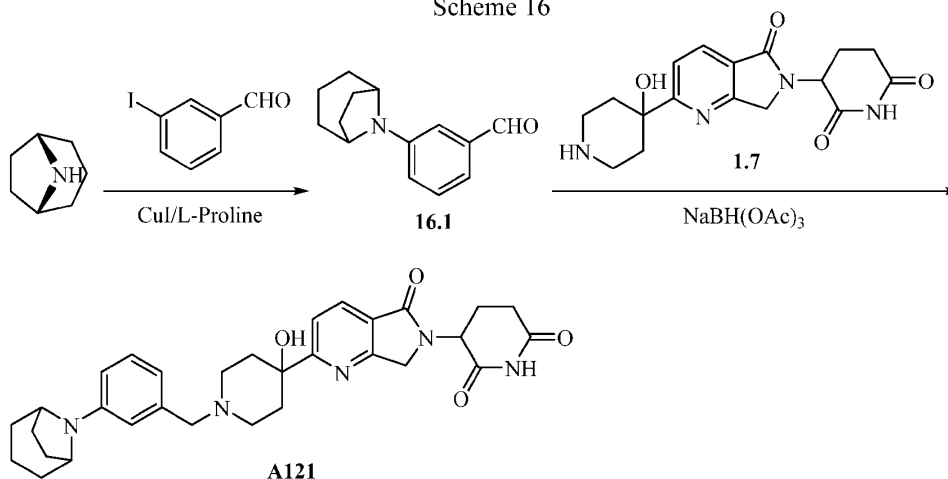
EXAMPLE 16

Synthesis of 3-(2-(1-((3-((1*R*,5*S*)-8-azabicyclo[3.2.1]octan-8-yl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A121**

**A121**

[0394] Compound **A121** was prepared as shown in Scheme 16.

Scheme 16

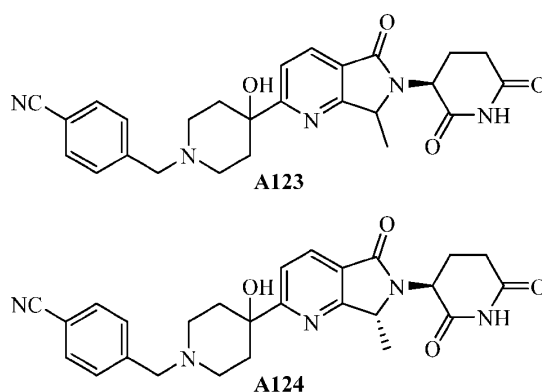


[0395] Preparation of 3-(8-azabicyclo[3.2.1]octan-8-yl)benzaldehyde **16.1**. To a solution of 8-azabicyclo[3.2.1]octane as a HCl salt (254 mg, 1.72 mmol) in DMF (4.00 mL) were added 3-iodobenzaldehyde (400 mg, 1.72 mmol), CuI (164 mg, 862 μ mol), L-proline (198 mg, 1.72 mmol), and K_2CO_3 (714 mg, 5.17 mmol). After stirring at 80 °C for 12 h under N_2 , the reaction mixture was filtered through celite, concentrated, and purified by column chromatography (SiO_2 , EtOAc/PE) to afford compound **2.1** (100 mg) in 13% yield. 1H NMR (400 MHz, $DMSO-d_6$) δ 9.90 (s, 1H), 7.40-7.36 (m, 1H), 7.23 (s, 1H), 7.14-7.08 (m, 2H), 4.26 (s, 2H), 2.00-1.98 (m, 2H), 1.86-1.80 (m, 3H), 1.76-1.69 (m, 2H), 1.43-1.38 (m, 1H), 1.29-1.23 (m, 2H); MS (ESI) m/z : 216.2 $[M+H]^+$.

[0396] Preparation of 3-(2-(1-((3-((1*R*,5*S*)-8-azabicyclo[3.2.1]octan-8-yl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A121**. To a solution of compound **16.1** (100 mg, 225 μ mol) in DMF (1.00 mL) were added 3-(2-(4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **1.7** as a HCl salt (85.7 mg, 225 μ mol) and NaBH(OAc)₃ (143 mg, 675 μ mol). After stirring at 40 °C for 12 h, the reaction mixture was diluted with H₂O (0.5 mL) and purified by prep-HPLC (C18, ACN in water containing 0.225% FA) to afford compound **A121** (40 mg) in 31% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.01 (s, 1H), 8.17 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.14-7.08 (m, 1H), 6.72 (s, 1H), 6.65-6.56 (m, 2H), 5.28 (s, 1H), 5.19-5.14 (m, 1H), 4.52-4.48 (m, 1H), 4.34-4.30 (m, 1H), 4.17 (s, 2H), 3.46 (m, 2H), 2.96-2.87 (m, 1H), 2.70-2.58 (m, 3H), 2.45-2.40 (m, 3H), 2.24-2.18 (m, 2H), 2.03-1.95 (m, 3H), 1.84-1.73 (m, 5H) 1.56-1.53 (m, 2H), 1.39-1.37 (m, 1H), 1.24-1.21 (m, 2H); MS (ESI) *m/z*: 544.3 [M+H]⁺.

EXAMPLE 17

Synthesis of 4-((4-(6-((*S*)-2,6-dioxopiperidin-3-yl)-7-methyl-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile **A123** and 4-((4-(6-((*R*)-2,6-dioxopiperidin-3-yl)-7-methyl-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile **A124**

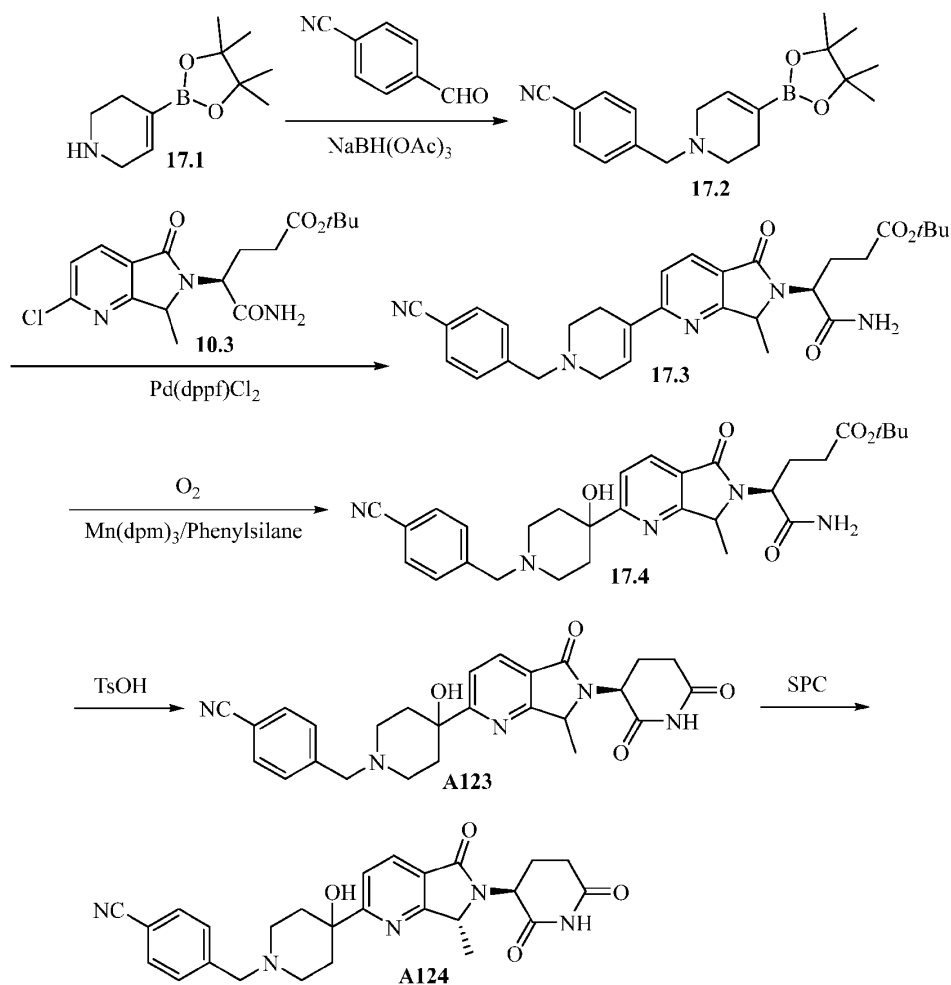


[0397] Compounds **A123** and **A124** were prepared as shown in Scheme 17.

[0398] Preparation of 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridin-1(2*H*)-yl)methyl)benzonitrile **17.2**. To a solution of 4-formylbenzonitrile (4 g, 30.5 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine **17.1** (6.38 g, 30.5 mmol) in DCM (20 mL) and THF (50 mL) was added NaBH(OAc)₃ (19.3 g, 91.5 mmol). After

stirring for 2 h, the reaction mixture was filtered and concentrated to afford compound **17.2** (10 g), which was used directly in the next step without further purification. MS (ESI) m/z : 325.1 $[M+H]^+$.

Scheme 17



[0399] Preparation of *tert*-butyl (4*S*)-5-amino-4-(2-(1-(4-cyanobenzyl)-1,2,3,6-tetrahydropyridin-4-yl)-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-5-oxopentanoate **17.3**. A solution of compound **17.2** (10 g, 30.8 mmol) and *tert*-butyl (4*S*)-5-amino-4-(2-chloro-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-5-oxopentanoate **10.3** (4 g, 10.8 mmol) in dioxane (80 mL) and H_2O (20 mL) were added K_2CO_3 (13.5 g, 97.8 mmol) and

Pd(dppf)Cl₂·CH₂Cl₂ (1.07 g, 1.30 mmol). After stirring at 50 °C for 12 h, the reaction mixture was diluted with H₂O (200 mL) and extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with brine (2 x 300 mL), dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography (SiO₂, EtOAc/PE) to afford compound **17.3** (3.9 g) in 59% yield. MS (ESI) *m/z*: 530.4 [M+H]⁺.

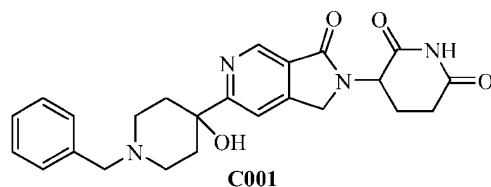
[0400] Preparation of *tert*-butyl (4*S*)-5-amino-4-(2-(1-(4-cyanobenzyl)-4-hydroxypiperidin-4-yl)-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-5-oxopentanoate **17.4**. A solution of compound **17.3** (3.90 g, 6.4 mmol) in IPA (39 mL), DCM (19 mL), and DMF (7 mL) were added Mn(dpm)₃ (386 mg, 639 μmol) and phenylsilane (1.38 g, 12.8 mmol). After stirring under O₂ (15 psi) for 2 h, the reaction mixture was poured into sat. aq. Na₂SO₃ (150 mL) at 10 °C and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (2 x 300 mL), dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by column chromatography (SiO₂, MeOH/EtOAc) to afford compound **17.4** (2.1 g) in 57% yield. MS (ESI) *m/z*: 548.3 [M+H]⁺.

[0401] Preparation of 4-((4-(6-((*S*)-2,6-dioxopiperidin-3-yl)-7-methyl-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile **A123**. A solution of compound **17.4** (2.1 g, 3.65 mmol) in ACN (20 mL) was added TsOH (1.89 g, 10.9 mmol). After stirring at 50 °C for 16 h, the reaction mixture was diluted with ACN (1 mL), neutralized to pH 5 - 6 with TEA in ACN, filtered, and purified by prep-HPLC (C18, ACN in water containing 10 mM NH₄HCO₃) to afford compound **A123** (1 g) in 55% yield. MS (ESI) *m/z*: 474.2 [M+H]⁺.

[0402] Synthesis of 4-((4-((*R*)-6-((*S*)-2,6-dioxopiperidin-3-yl)-7-methyl-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile **A124**. Compound **A123** (1 g, 2.01 mmol) was resolved by SFC isocratically using a DAICEL CHIRALPAK AD chiral column and further purified by prep-HPLC (C18, ACN in water containing 0.225% FA) to afford compound **A124** (211 mg) in 20% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.9 (s, 1H), 8.15 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.84-7.79 (m, 3H), 7.56 (d, *J* = 8.0 Hz, 2H), 5.51-5.14 (m, 1H), 4.84-4.80 (m, 1H), 4.67 (q, *J* = 6.6 Hz, 1H), 3.62 (s, 2H), 2.89-2.81 (m, 1H), 2.68-2.58 (m, 4H), 2.47-2.44 (m, 2H), 2.31-2.19 (m, 2H), 2.05-2.00 (m, 1H), 1.55 (d, *J* = 12.0 Hz, 2H), 1.45 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z*: 474.2 [M+H]⁺.

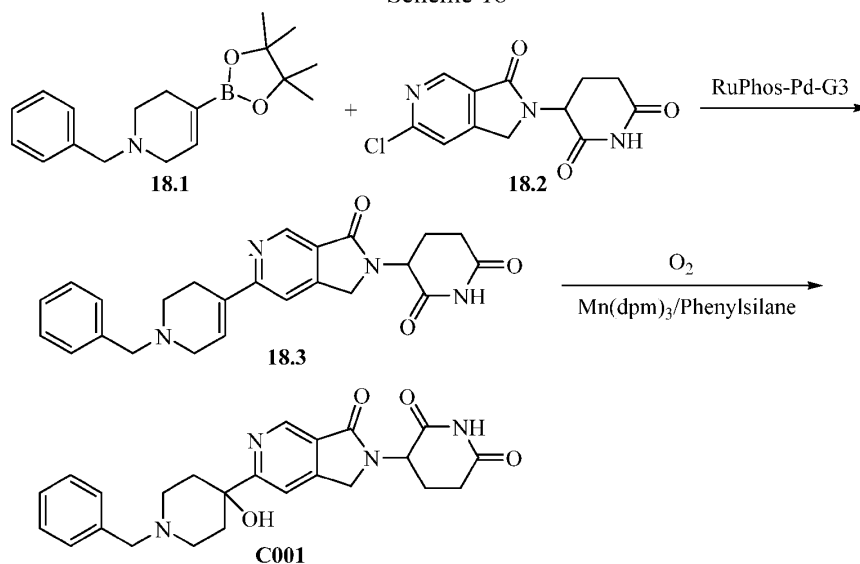
EXAMPLE 18

Synthesis of 3-(6-(1-benzyl-4-hydroxypiperidin-4-yl)-3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)piperidine-2,6-dione **C001**



[0403] Compound **C001** was prepared as shown in Scheme 18.

Scheme 18



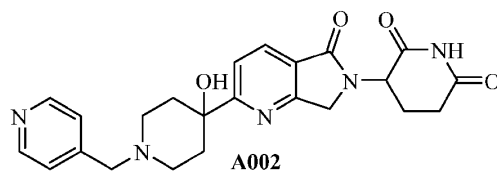
[0404] Preparation of 3-(6-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)piperidine-2,6-dione **18.3**. To a solution of 1-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine **18.1** (2.08 g, 6.94 mmol) and 3-(6-chloro-3-oxo-1*H*-pyrrolo[3,4-*c*]pyridin-2-yl)piperidine-2,6-dione **18.2** (1 g, 3.47 mmol) in dioxane (10 mL) and H₂O (0.5 mL) were added K₃PO₄ (883 mg, 4.16 mmol) and RuPhos-Pd-G3 (290 mg, 346 μmol) at 25 °C under N₂. After stirring at 100 °C for 2 h, the reaction mixture was concentrated and purified by column chromatography (SiO₂, MeOH/DCM) to afford compound **18.3** (700 mg) in 48% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.86 (s, 1H), 7.77 (s, 1H), 7.35-7.24 (m, 5H), 6.86 (s, 1H), 5.14-5.10 (m, 1H), 4.54-4.36 (m, 2H), 3.61 (s, 2H),

3.15-3.14 (m, 2H), 2.95-2.86 (m, 1H), 2.67-2.66 (m, 2H), 2.62 (s, 2H), 2.45-2.32 (m, 2H), 2.02-1.98 (m, 1H); MS (ESI) m/z : 417.0 $[M+H]^+$.

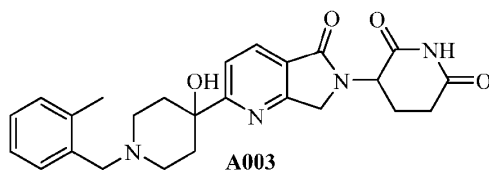
[0405] Preparation of 3-(6-(1-benzyl-4-hydroxypiperidin-4-yl)-3-oxo-1,3-dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)piperidine-2,6-dione **C001**. To a solution of compound **18.3** (200 mg, 476 μ mol) in DCM (6 mL), DMF (1.2 mL), and IPA (6 mL) was added phenylsilane (103 mg, 952 μ mol) at 25 °C, followed by addition of Mn(dpm)₃ (144 mg, 238 μ mol) at 0 °C. After stirring at 25 °C for 12 h under O₂, the reaction mixture was concentrated, purified by column chromatography (SiO₂, MeOH/DCM) and prep-HPLC (C18, ACN in water containing 0.05% TFA) to afford compound **C001** (25.7 mg) in 12% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 9.59-9.52 (m, 1H), 8.93-8.88 (m, 1H), 7.96 (s, 1H), 7.57-7.49 (m, 5H), 5.92-5.91 (m, 1H), 5.15-5.11 (m, 1H), 4.60-4.53 (m, 1H), 4.44-4.40 (m, 3H), 3.34-3.24 (m, 4H), 2.95-2.86 (m, 1H), 2.66-2.58 (m, 1H), 2.45-2.31 (m, 3H), 2.02-1.99 (m, 1H), 1.82-1.78 (m, 2H); MS (ESI) m/z : 435.2 $[M+H]^+$.

[0406] The following compounds were prepared similarly according to the synthetic procedures or methodologies exemplified herein.

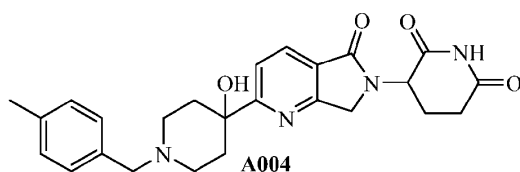
[0407] 3-(2-(4-Hydroxy-1-(pyridin-4-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A002**. MS (ESI) m/z : 436.3 $[M+H]^+$.



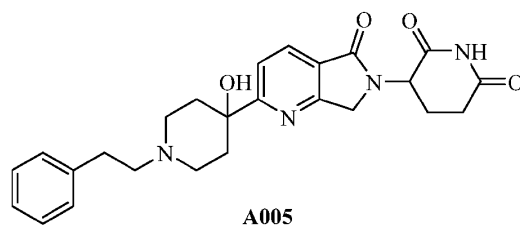
[0408] 3-(2-(4-Hydroxy-1-(2-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A003**. MS (ESI) m/z : 449.3 $[M+H]^+$.



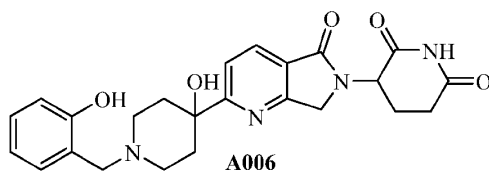
[0409] 3-(2-(4-Hydroxy-1-(4-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A004**. MS (ESI) m/z : 449.3 $[M+H]^+$.



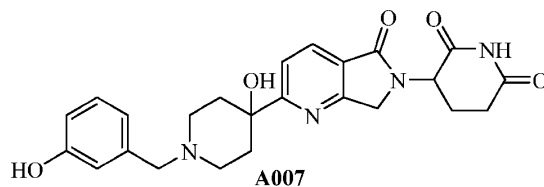
[0410] 3-(2-(4-Hydroxy-1-phenethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]-pyridin-6-yl)piperidine-2,6-dione **A005**. MS (ESI) *m/z*: 449.3 [M+H]⁺.



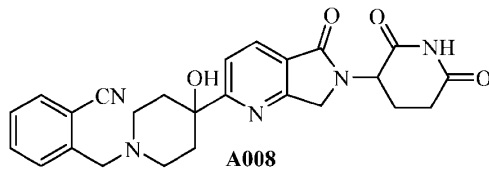
[0411] 3-(2-(4-Hydroxy-1-(2-hydroxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A006**. MS (ESI) *m/z*: 451.2 [M+H]⁺.



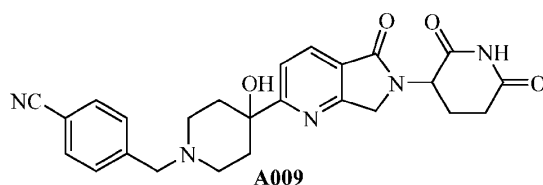
[0412] 3-(2-(4-Hydroxy-1-(3-hydroxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A007**. MS (ESI) *m/z*: 451.2 [M+H]⁺.



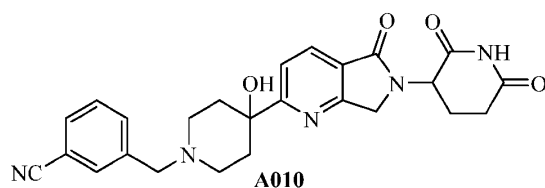
[0413] 3-(2-(4-Hydroxy-1-(2-cyanobenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A008**. MS (ESI) *m/z*: 460.2 [M+H]⁺.



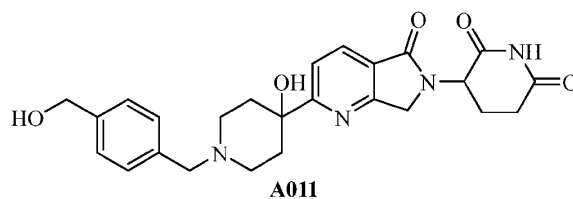
[0414] 3-(2-(4-Hydroxy-1-(4-cyanobenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A009**. MS (ESI) *m/z*: 460.2 [M+H]⁺.



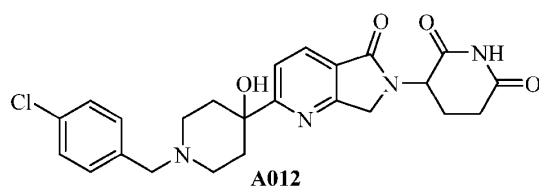
[0415] 3-(2-(4-Hydroxy-1-(3-cyanobenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A010**. MS (ESI) *m/z*: 460.2 [M+H]⁺.



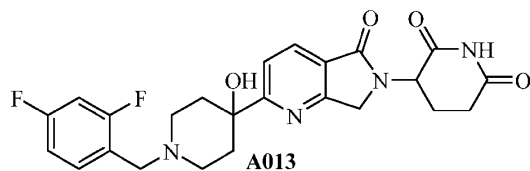
[0416] 3-(2-(4-Hydroxy-1-(4-(hydroxymethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A011**. MS (ESI) *m/z*: 465.3 [M+H]⁺.



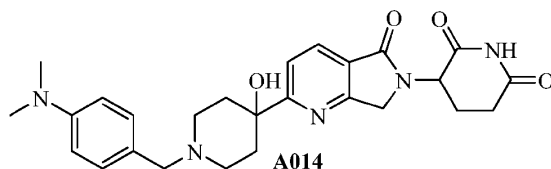
[0417] 3-(2-(1-(4-Chlorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A012**. MS (ESI) *m/z*: 469.2 [M+H]⁺.



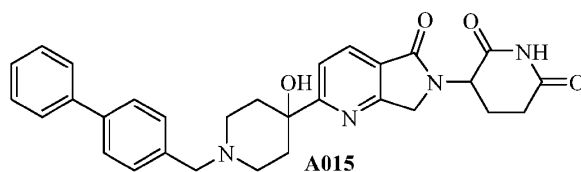
[0418] 3-(2-(1-(2,4-Difluorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A013**. MS (ESI) *m/z*: 471.2 [M+H]⁺.



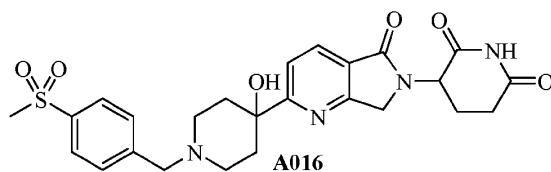
[0419] 3-(2-(1-(4-(Dimethylamino)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A014**. MS (ESI) *m/z*: 478.3 [M+H]⁺.



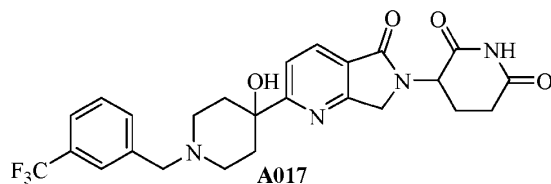
[0420] 3-(2-(1-([1,1'-Biphenyl]-4-ylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A015**. MS (ESI) *m/z*: 511.3 [M+H]⁺.



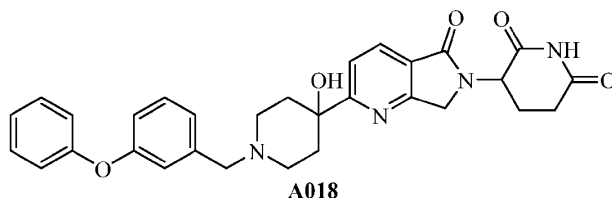
[0421] 3-(2-(4-Hydroxy-1-(4-(methylsulfonyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A016**. MS (ESI) *m/z*: 513.3 [M+H]⁺.



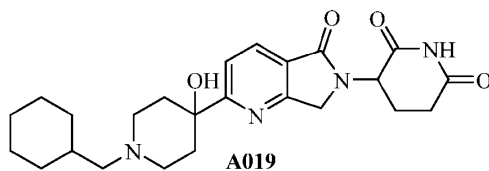
[0422] 3-(2-(4-Hydroxy-1-(3-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A017**. MS (ESI) *m/z*: 503.2 [M+H]⁺.



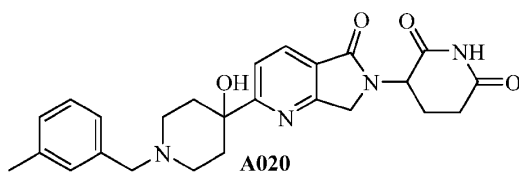
[0423] 3-(2-(4-Hydroxy-1-(3-phenoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A018**. MS (ESI) *m/z*: 527.3 [M+H]⁺.



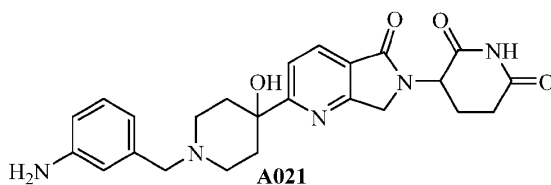
[0424] 3-(2-(1-(Cyclohexylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A019**. MS (ESI) *m/z*: 441.3 [M+H]⁺.



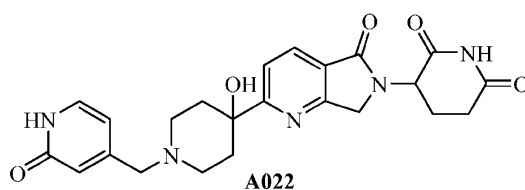
[0425] 3-(2-(4-Hydroxy-1-(3-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A020**. MS (ESI) *m/z*: 449.3 [M+H]⁺.



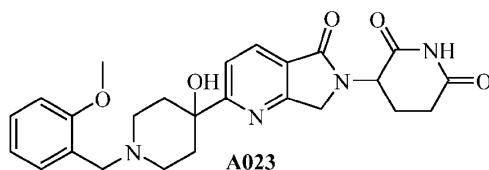
[0426] 3-(2-(1-(3-Aminobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A021**. MS (ESI) *m/z*: 450.3 [M+H]⁺.



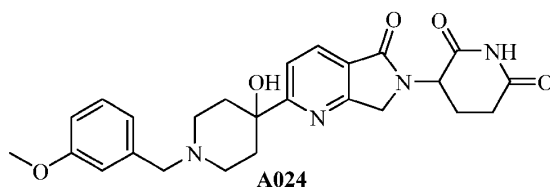
[0427] 3-(2-(4-Hydroxy-1-((2-oxo-1,2-dihydropyridin-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A022**. MS (ESI) *m/z*: 452.2 [M+H]⁺.



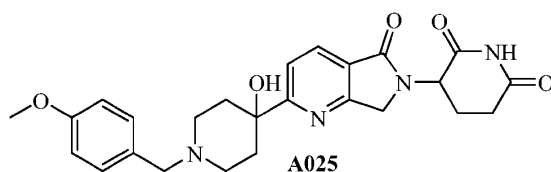
[0428] 3-(2-(4-Hydroxy-1-(2-methoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A023**. MS (ESI) *m/z*: 465.3 [M+H]⁺.



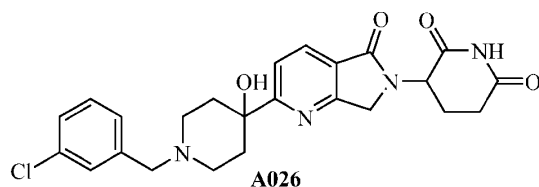
[0429] 3-(2-(4-Hydroxy-1-(3-methoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo-[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A024**. MS (ESI) m/z : 465.3 $[M+H]^+$.



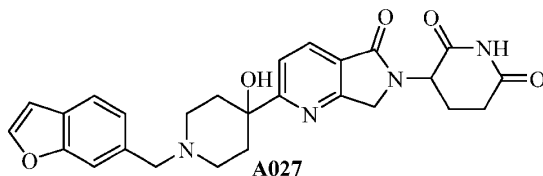
[0430] 3-(2-(4-Hydroxy-1-(4-methoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo-[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A025**. MS (ESI) m/z : 465.2 $[M+H]^+$.



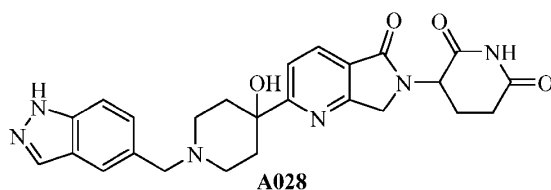
[0431] 3-(2-(1-(3-Chlorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A026**. MS (ESI) m/z : 469.2 $[M+H]^+$.



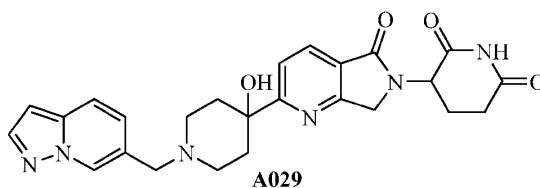
[0432] 3-(2-(1-(Benzofuran-6-ylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A027**. MS (ESI) m/z : 475.3 $[M+H]^+$.



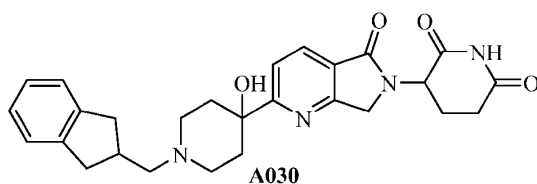
[0433] 3-(2-(1-((1*H*-Indazol-5-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A028**. MS (ESI) m/z : 475.3 $[M+H]^+$.



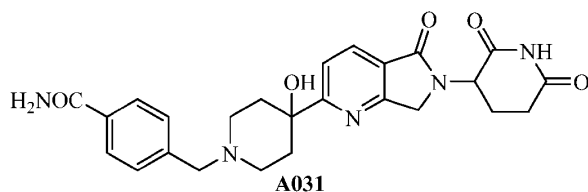
[0434] 3-(2-(4-Hydroxy-1-(pyrazolo[1,5-*a*]pyridin-6-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A029**. MS (ESI) *m/z*: 475.3 [M+H]⁺.



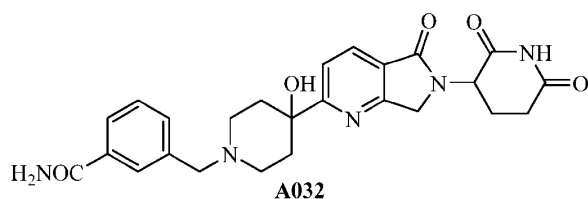
[0435] 3-(2-(1-((2,3-Dihydro-1*H*-inden-2-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A030**. MS (ESI) *m/z*: 475.3 [M+H]⁺.



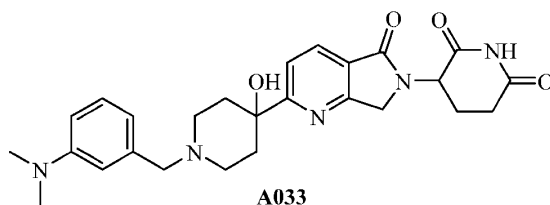
[0436] 3-(2-(4-Hydroxy-1-(4-aminocarbonylphenyl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A031**. MS (ESI) *m/z*: 478.3 [M+H]⁺.



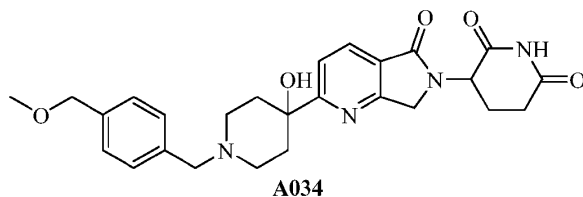
[0437] 3-(2-(4-Hydroxy-1-(3-aminocarbonylphenyl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A032**. MS (ESI) *m/z*: 478.3 [M+H]⁺.



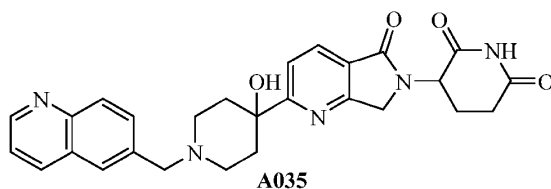
[0438] 3-(2-(1-(3-(Dimethylamino)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A033**. MS (ESI) *m/z*: 478.3 [M+H]⁺.



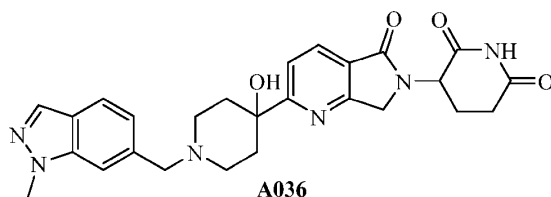
[0439] 3-(2-(4-Hydroxy-1-(4-(methoxymethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A034**. MS (ESI) *m/z*: 479.3 [M+H]⁺.



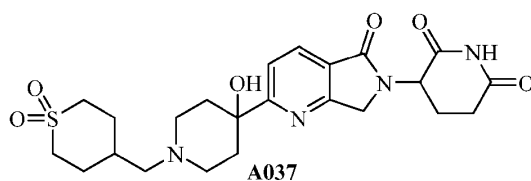
[0440] 3-(2-(4-Hydroxy-1-(quinolin-6-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A035**. MS (ESI) *m/z*: 486.5 [M+H]⁺.



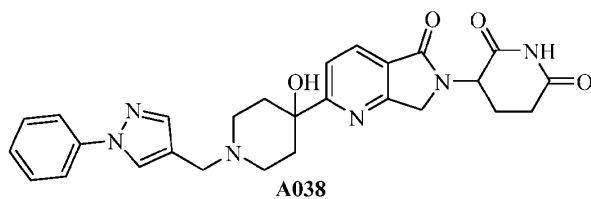
[0441] 3-(2-(4-Hydroxy-1-((1-methyl-1*H*-indazol-6-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A036**. MS (ESI) *m/z*: 489.3 [M+H]⁺.



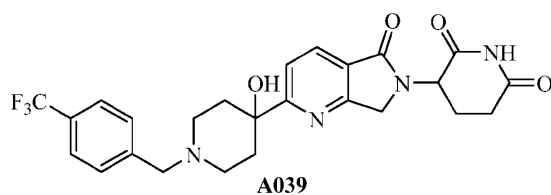
[0442] 3-(2-(1-((1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A037**. MS (ESI) *m/z*: 491.3 [M+H]⁺.



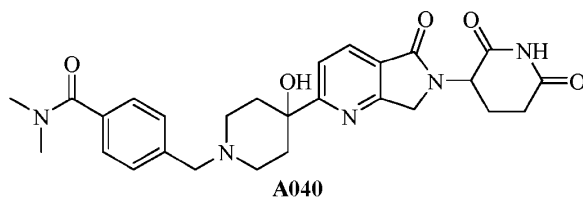
[0443] 3-(2-(4-Hydroxy-1-((1-phenyl-1*H*-pyrazol-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A038**. MS (ESI) *m/z*: 501.3 [M+H]⁺.



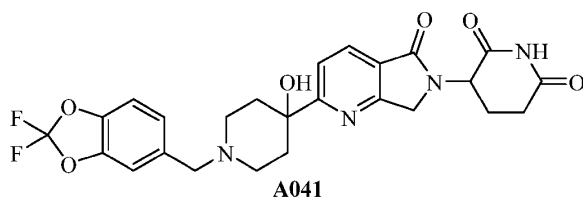
[0444] 3-(2-(4-Hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A039**. MS (ESI) *m/z*: 503.2 [M+H]⁺.



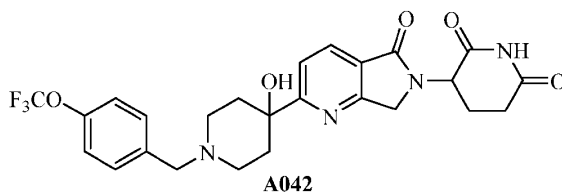
[0445] 4-((4-(6-(2,6-Dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)-*N,N*-dimethylbenzamide **A040**. MS (ESI) *m/z*: 506.3 [M+H]⁺.



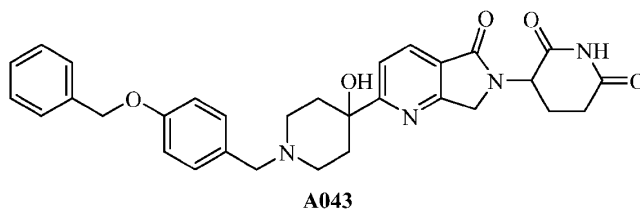
[0446] 3-(2-(1-((2,2-Difluorobenzo[d][1,3]dioxol-5-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A041**. MS (ESI) m/z : 515.3 $[M+H]^+$.



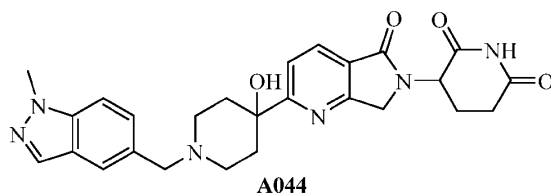
[0447] 3-(2-(4-Hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A042**. MS (ESI) m/z : 519.2 $[M+H]^+$.



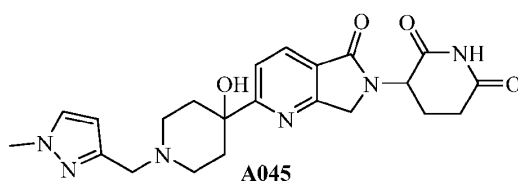
[0448] 3-(2-(1-(4-(Benzyloxy)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A043**. MS (ESI) m/z : 541.3 $[M+H]^+$.



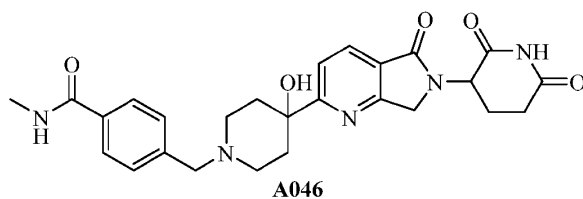
[0449] 3-(2-(4-Hydroxy-1-((1-methyl-1H-indazol-5-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A044**. MS (ESI) m/z : 489.2 $[M+H]^+$.



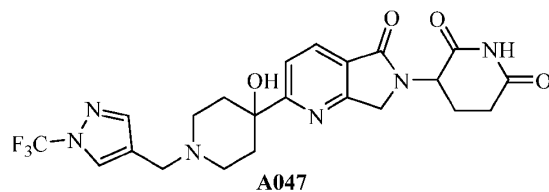
[0450] 3-(2-(4-Hydroxy-1-((1-methyl-1H-pyrazol-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A045**. MS (ESI) *m/z*: 439.6 [M+H]⁺.



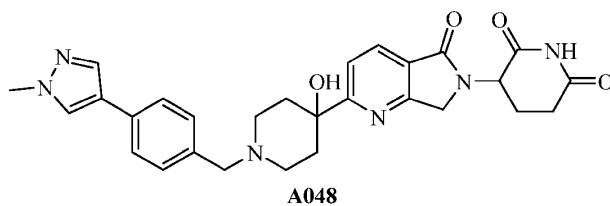
[0451] 4-((4-(6-(2,6-Dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)-*N*-methylbenzamide **A046**. MS (ESI) *m/z*: 492.3 [M+H]⁺.



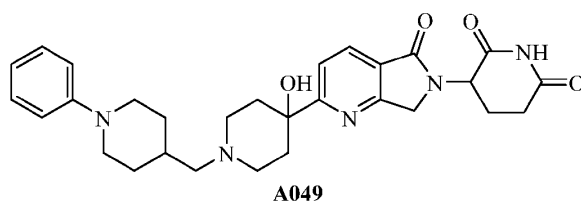
[0452] 3-(2-(4-Hydroxy-1-((1-(trifluoromethyl)-1H-pyrazol-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A047**. MS (ESI) *m/z*: 493.2 [M+H]⁺.



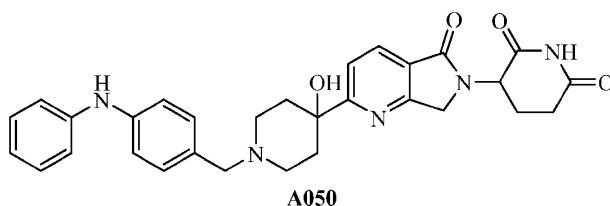
[0453] 3-(2-(4-Hydroxy-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A048**. MS (ESI) *m/z*: 515.3 [M+H]⁺.



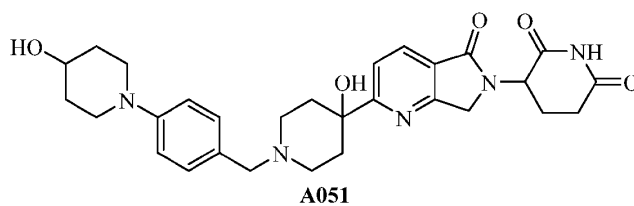
[0454] 3-(2-(4-Hydroxy-1-((1-phenylpiperidin-4-yl)methyl)piperidin-4-yl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A049**. MS (ESI) *m/z*: 518.3 [M+H]⁺.



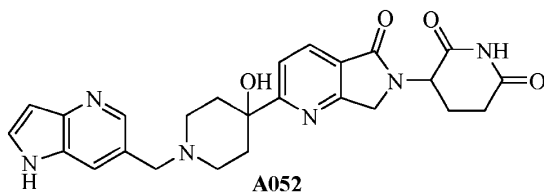
[0455] 3-(2-(4-Hydroxy-1-(4-(phenylamino)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A050**. MS (ESI) *m/z*: 526.3 [M+H]⁺.



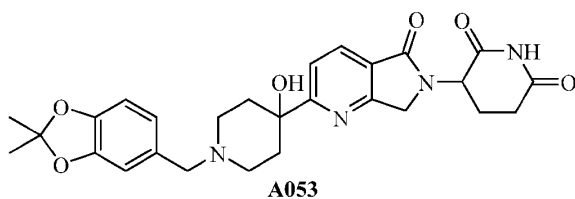
[0456] 3-(2-(4-Hydroxy-1-(4-(4-hydroxypiperidin-1-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A051**. MS (ESI) *m/z*: 534.3 [M+H]⁺.



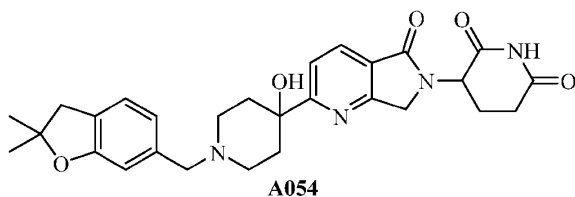
[0457] 3-(2-(1-((1H-Pyrrolo[3,2-*b*]pyridin-6-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A052**. MS (ESI) *m/z*: 475.2 [M+H]⁺.



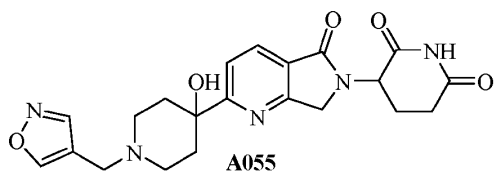
[0458] 3-(2-(1-((2,2-Dimethylbenzo[d][1,3]dioxol-5-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A053**. MS (ESI) *m/z*: 507.3 [M+H]⁺.



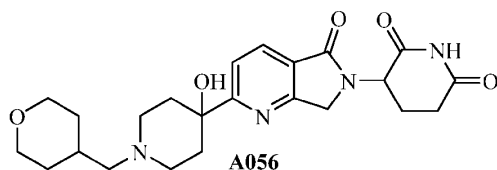
[0459] 3-(2-(1-((2,2-Dimethyl-2,3-dihydrobenzofuran-6-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A054**. MS (ESI) *m/z*: 505.3 [M+H]⁺.



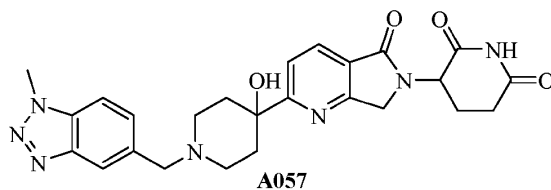
[0460] 3-(2-(4-Hydroxy-1-(isoxazol-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A055**. MS (ESI) *m/z*: 426.2 [M+H]⁺.



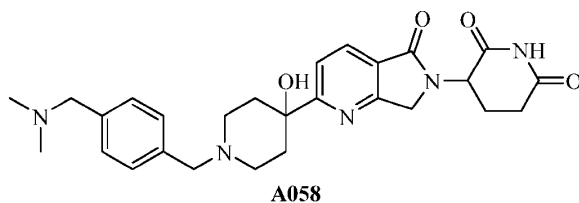
[0461] 3-(2-(4-Hydroxy-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A056**. MS (ESI) *m/z*: 443.3 [M+H]⁺.



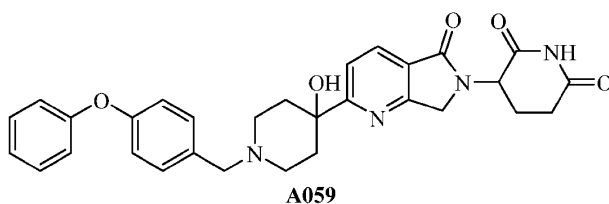
[0462] 3-(2-(4-Hydroxy-1-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A057**. MS (ESI) *m/z*: 490.3 [M+H]⁺.



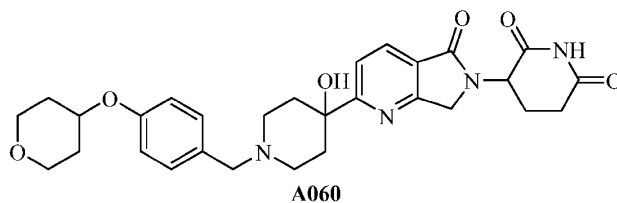
[0463] 3-(2-(1-(4-((Dimethylamino)methyl)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A058**. MS (ESI) *m/z*: 492.4 [M+H]⁺.



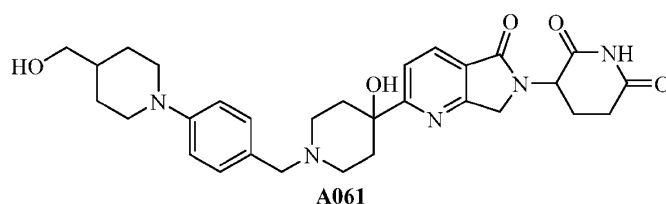
[0464] 3-(2-(4-Hydroxy-1-(4-phenoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A059**. MS (ESI) *m/z*: 527.3 [M+H]⁺.



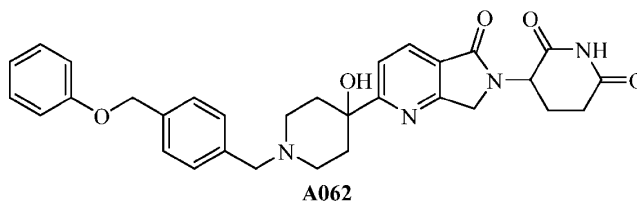
[0465] 3-(2-(4-Hydroxy-1-(4-((tetrahydro-2H-pyran-4-yl)oxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A060**. MS (ESI) *m/z*: 535.3 [M+H]⁺.



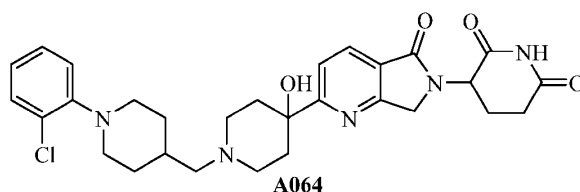
[0466] 3-(2-(4-Hydroxy-1-(4-(4-(hydroxymethyl)piperidin-1-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A061**. MS (ESI) m/z : 548.3 $[M+H]^+$.



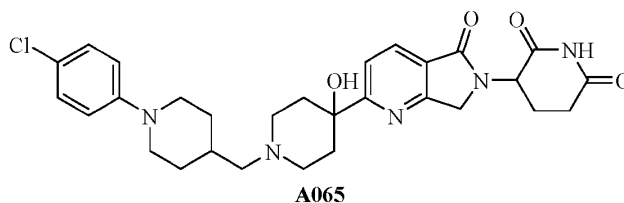
[0467] 3-(2-(4-Hydroxy-1-(4-(phenoxymethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A062**. MS (ESI) m/z : 541.3 $[M+H]^+$.



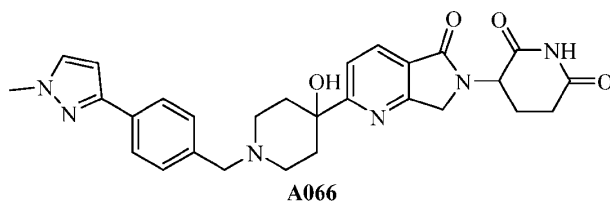
[0468] 3-(2-(1-((1-(2-Chlorophenyl)-4-piperidyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A064**. 1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.18 (s, 1H), 8.13 (d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.30-7.2 (m, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 7.00 (t, $J = 7.6$ Hz, 1H), 5.31-5.22 (m, 1H), 5.19-5.14 (m, 1H), 4.49 (d, $J = 17.6$ Hz, 1H), 4.32 (d, $J = 17.6$ Hz, 1H), 3.27 (d, $J = 11.4$ Hz, 2H), 2.96-2.87 (m, 1H), 2.71 (d, $J = 10.0$ Hz, 2H), 2.65-2.59 (m, 3H), 2.45-2.37 (m, 3H), 2.28-2.20 (m, 4H), 2.03-2.01 (m, 1H), 1.84 (d, $J = 12.0$ Hz, 2H), 1.74-1.63 (m, 1H), 1.60-1.53 (m, 2H), 1.33-1.25 (m, 2H); MS (ESI) m/z : 552.4 $[M+H]^+$.



[0469] 3-(2-(1-((1-(4-Chlorophenyl)piperidin-4-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A065**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.19 (d, $J = 9.0$ Hz, 2H), 6.93 (d, $J = 9.1$ Hz, 2H), 5.25 (s, 1H), 5.19-5.14 (m, 1H), 4.49 (d, $J = 18.0$ Hz, 1H), 4.32 (d, $J = 17.6$ Hz, 1H), 3.66 (d, $J = 12.0$ Hz, 2H), 2.96-2.87 (m, 1H), 2.67-2.58 (m, 5H), 2.43 (m, 1H), 2.37-2.32 (m, 2H), 2.24-2.18 (m, 4H), 2.04-1.99 (m, 1H), 1.80 (d, $J = 12.0$ Hz, 2H), 1.68-1.66 (m, 1H), 1.55-1.51 (m, 2H), 1.23-1.13 (m, 2H); MS (ESI) m/z : 552.3 $[\text{M}+\text{H}]^+$.

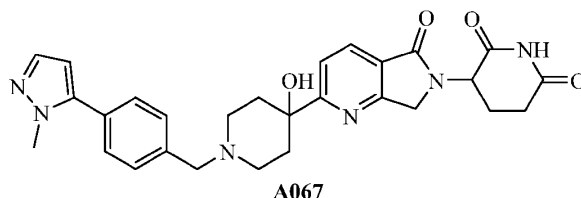


[0470] 3-(2-(4-Hydroxy-1-((4-(1-methylpyrazol-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A066**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.17 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.74-7.70 (m, 3H), 7.35 (d, $J = 8.0$ Hz, 2H), 6.65 (d, $J = 2.0$ Hz, 1H), 5.32-5.23 (m, 1H), 5.19-5.14 (m, 1H), 4.50 (d, $J = 17.6$ Hz, 1H), 4.33 (d, $J = 17.8$ Hz, 1H), 3.87 (s, 3H), 3.54 (s, 2H), 2.96-2.87 (m, 1H), 2.69-2.58 (m, 4H), 2.44-2.41 (m, 2H), 2.26-2.18 (m, 2H), 2.04-2.00 (m, 1H), 1.57-1.53 (m, 2H); MS (ESI) m/z : 515.3 $[\text{M}+\text{H}]^+$.

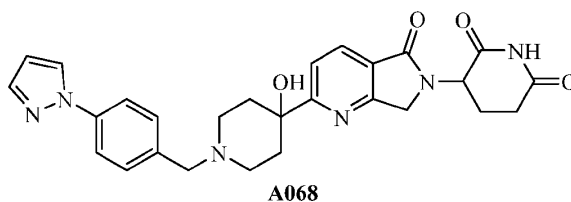


[0471] 3-(2-(4-Hydroxy-1-((4-(2-methylpyrazol-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A067**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.03-10.93 (m, 1H), 8.20 (s, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.50-7.45 (m, 5H), 6.39 (d, $J = 2.0$ Hz, 1H), 5.19-5.14 (m, 2H), 4.52-4.31 (m, 2H), 3.85 (s, 3H), 3.58 (s, 2H), 2.92-

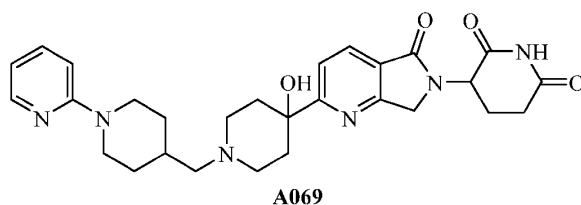
2.89 (m, 1H), 2.71-2.86 (m, 2H), 2.63-2.58 (m, 1H), 2.47-2.41 (m, 3H), 2.27-2.21 (m, 2H), 2.05-2.00 (m, 1H), 1.58-1.54 (m, 2H); MS (ESI) m/z : 515.3 $[M+H]^+$.



[0472] 3-(2-(4-Hydroxy-1-((4-pyrazol-1-ylphenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A068**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.35-10.69 (m, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.21 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 1.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 6.54-6.53 (m, 1H), 5.21-5.15 (m, 2H), 4.53-4.31 (m, 2H), 3.57 (s, 2H), 2.97-2.88 (m, 1H), 2.70-2.67 (m, 2H), 2.64-2.59 (m, 1H), 2.46-2.38 (m, 3H), 2.27-2.20 (m, 2H), 2.05-2.01 (m, 1H), 1.58-1.54 (m, 2H); MS (ESI) m/z : 501.2 $[M+H]^+$.

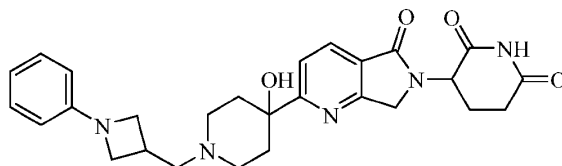


[0473] 3-(2-(4-Hydroxy-1-((1-(2-pyridyl)-4-piperidyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A069**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.26 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.08-8.06 (m, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.50-7.45 (m, 1H), 6.78 (d, J = 4.8 Hz, 1H), 6.57-6.53 (m, 1H), 5.19-5.14 (m, 1H), 4.50 (d, J = 17.6 Hz, 1H), 4.35-4.25 (m, 3H), 2.97-2.88 (m, 1H), 2.82-2.59 (m, 5H), 2.42-2.30 (m, 3H), 2.25-2.19 (m, 4H), 2.10-1.98 (m, 1H), 1.80-1.74 (m, 3H), 1.56-1.52 (m, 2H), 1.13-1.04 (m, 2H); MS (ESI) m/z : 519.4 $[M+H]^+$.



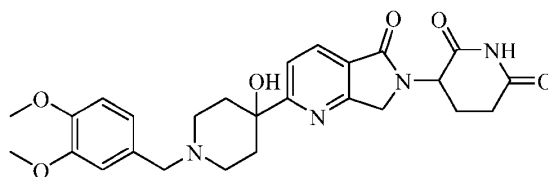
[0474] 3-(2-(4-Hydroxy-1-((1-phenylazetidin-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A073**. ^1H NMR (400 MHz, DMSO- d_6) δ

11.0 (s, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.15 (t, $J = 7.2$ Hz, 2H), 6.64 (t, $J = 7.2$ Hz, 1H), 6.41 (d, $J = 7.6$ Hz, 2H), 5.26 (s, 1H), 5.17-5.14 (m, 1H), 4.54-4.29 (m, 2H), 3.91 (t, $J = 7.2$ Hz, 2H), 3.47-3.43 (m, 2H), 2.97-2.87 (m, 2H), 2.70-2.67 (m, 2H), 2.64-2.57 (m, 3H), 2.45-2.36 (m, 3H), 2.26-2.16 (m, 2H), 2.09-1.98 (m, 1H), 1.56-1.52 (m, 2H); MS (ESI) m/z : 490.2 $[M+H]^+$.



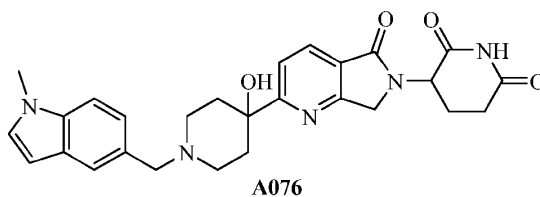
A073

[0475] 3-(2-(1-(3,4-Dimethoxybenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A075**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.17 (s, 1H), 8.14-8.12 (m, 1H), 7.85-7.83 (m, 1H), 6.93-6.84 (m, 3H), 5.54-5.29 (m, 1H), 5.24-5.14 (m, 1H), 4.52-4.47 (m, 1H), 4.34-4.30 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.52 (s, 2H), 2.96-2.87 (m, 1H), 2.72-2.70 (m, 2H), 2.63-2.58 (m, 1H), 2.47-2.44 (m, 2H), 2.42-2.32 (m, 1H), 2.26-2.20 (m, 2H), 2.07-2.00 (m, 1H), 1.58-1.54 (m, 2H); MS (ESI) m/z : 495.4 $[M+H]^+$.

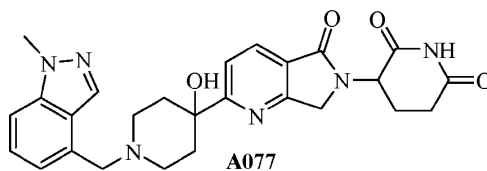


A075

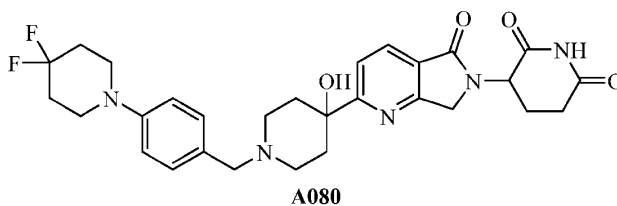
[0476] 3-(2-(4-Hydroxy-1-((1-methylindol-5-yl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A076**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.18 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.4$ Hz, 1H), 7.48 (s, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 7.28 (d, $J = 3.2$ Hz, 1H), 7.17-7.14 (m, 1H), 6.38 (d, $J = 2.8$ Hz, 1H), 5.42-5.26 (m, 1H), 5.25-5.14 (m, 1H), 4.49 (d, $J = 17.6$ Hz, 1H), 4.32 (d, $J = 17.6$ Hz, 1H), 3.77 (s, 3H), 3.65 (s, 2H), 2.96-2.87 (m, 1H), 2.74-2.71 (m, 2H), 2.62-2.58 (m, 1H), 2.45-2.38 (m, 3H), 2.25-2.19 (m, 2H), 2.03-2.00 (m, 1H), 1.57-1.53 (m, 2H); MS (ESI) m/z : 488.2 $[M+H]^+$.



[0477] 3-(2-(4-Hydroxy-1-((1-methylindazol-4-yl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A077**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.0 (s, 1H), 8.23 (d, $J = 0.8$ Hz, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 1H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.35-7.31 (m, 1H), 7.08 (d, $J = 6.8$ Hz, 1H), 5.25 (s, 1H), 5.18-5.14 (m, 1H), 4.51 (d, $J = 17.6$ Hz, 1H), 4.32 (d, $J = 18.0$ Hz, 1H), 4.03 (s, 3H), 3.82 (s, 2H), 2.96-2.87 (m, 1H), 2.69-2.57 (m, 3H), 2.47-2.40 (m, 3H), 2.27-2.17 (m, 2H), 2.04-2.00 (m, 1H), 1.56-1.51 (m, 2H); MS (ESI) m/z : 489.1 $[\text{M}+\text{H}]^+$.

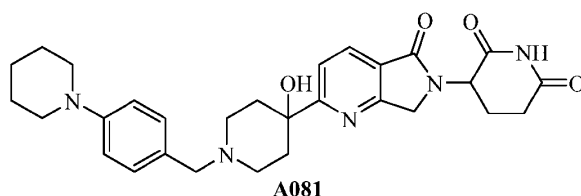


[0478] 3-(2-(1-((4-(4,4-Difluoro-1-piperidyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A080**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.0 (m, 1H), 8.19 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.83 (d, $J = 8.4$ Hz, 2H), 5.46-5.24 (m, 1H), 5.18-5.14 (m, 1H), 4.49 (d, $J = 17.6$ Hz, 1H), 4.49 (d, $J = 17.6$ Hz, 1H), 3.40 (s, 2H), 3.31-3.28 (m, 4H), 2.96-2.87 (m, 1H), 2.69-2.59 (m, 3H), 2.46-2.41 (m, 3H), 2.24-2.16 (m, 2H), 2.09-1.99 (m, 5H), 1.57-1.53 (m, 2H); MS (ESI) m/z : 554.3 $[\text{M}+\text{H}]^+$.

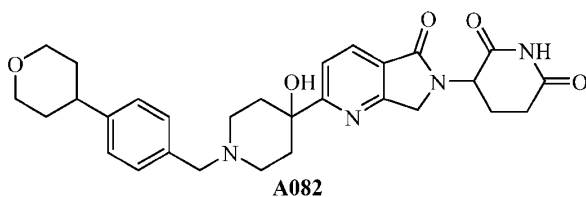


[0479] 3-(2-(4-Hydroxy-1-(4-(piperidin-1-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A081**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.0 (s, 1H), 8.18 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.15 (d, $J = 8.4$ Hz, 2H),

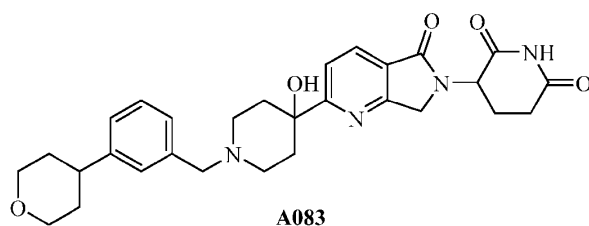
6.87 (d, $J = 8.4$ Hz, 2H), 5.35-5.25 (m, 1H), 5.24-5.14 (m, 1H), 4.49 (d, $J = 17.6$ Hz, 1H), 4.32 (d, $J = 17.6$ Hz, 1H), 3.45 (s, 2H), 3.11-3.08 (m, 4H), 2.96-2.87 (m, 1H), 2.69-2.58 (m, 3H), 2.45-2.39 (m, 3H), 2.23-2.17 (m, 2H), 2.04-2.00 (m, 1H), 1.63-1.51 (m, 8H); MS (ESI) m/z : 518.3 $[M+H]^+$.



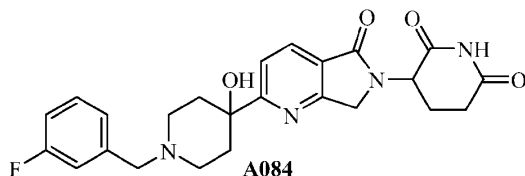
[0480] 3-(2-(4-Hydroxy-1-((4-tetrahydropyran-4-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A082**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.16 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.27-7.25 (m, 2H), 7.21-7.19 (m, 2H), 5.28-5.23 (m, 1H), 5.17-5.14 (m, 1H), 4.51-4.47 (m, 1H), 4.34-4.30 (m, 1H), 3.95-3.92 (m, 2H), 3.49 (s, 2H), 3.42 (d, $J = 3.2$ Hz, 2H), 2.95-2.87 (m, 1H), 2.74-2.71 (m, 1H), 2.70-2.63 (m, 3H), 2.45-2.38 (m, 3H), 2.24-2.18 (m, 2H), 2.07-2.00 (m, 1H), 1.69-1.63 (m, 4H), 1.55-1.52 (m, 2H); MS (ESI) m/z : 519.3 $[M+H]^+$.



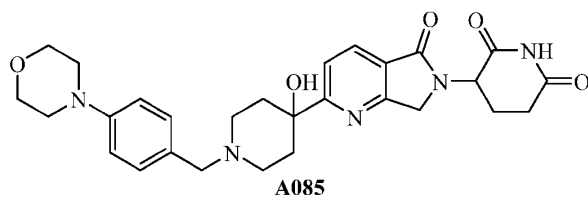
[0481] 3-(2-(4-Hydroxy-1-(3-(tetrahydro-2H-pyran-4-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A083**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.16 (s, 1H), 8.13 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.28-7.24 (m, 1H), 7.21 (s, 1H), 7.18-7.12 (m, 2H), 5.28-5.23 (m, 1H), 5.18-5.14 (m, 1H), 4.52-4.48 (m, 1H), 4.35-4.30 (m, 1H), 3.96-3.92 (m, 2H), 3.51 (s, 2H), 3.43 (d, $J = 3.2$ Hz, 2H), 2.95-2.87 (m, 1H), 2.80-2.73 (m, 1H), 2.67-2.65 (m, 3H), 2.45-2.37 (m, 3H), 2.25-2.18 (m, 2H), 2.07-2.00 (m, 1H), 1.70-1.63 (m, 4H), 1.56-1.52 (m, 2H); MS (ESI) m/z : 519.3 $[M+H]^+$.



[0482] 3-(2-(1-((3-Fluorophenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]-pyridin-6-yl)piperidine-2,6-dione **A084**. ^1H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.15-8.12 (m, 2H), 7.84 (d, J = 8.4 Hz, 1H), 7.39-7.34 (m, 1H), 7.20-7.15 (m, 2H), 7.09-7.04 (m, 1H), 5.42-5.24 (m, 1H), 5.19-5.14 (m, 1H), 4.49 (d, J = 17.6 Hz, 1H), 4.32 (d, J = 17.6 Hz, 1H), 3.56 (s, 2H), 2.96-2.87 (m, 1H), 2.67-2.59 (m, 3H), 2.45-2.38 (m, 3H), 2.26-2.20 (m, 2H), 2.05-2.01 (m, 1H), 1.57-1.53 (m, 2H); MS (ESI) m/z : 453.1 $[\text{M}+\text{H}]^+$.

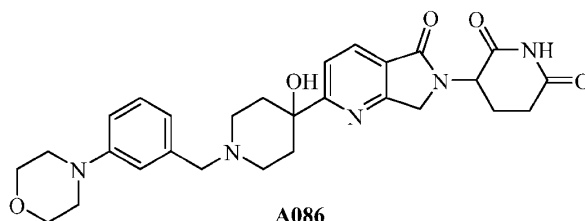


[0483] 3-(2-(4-Hydroxy-1-((4-morpholinophenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A085**. ^1H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.22 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.34-5.24 (m, 1H), 5.18-5.14 (m, 1H), 4.50 (d, J = 17.6 Hz, 1H), 4.32 (d, J = 17.6 Hz, 1H), 3.74-3.71 (m, 4H), 3.44 (s, 2H), 3.08-3.06 (m, 4H), 2.96-2.87 (m, 1H), 2.66-2.58 (m, 3H), 2.45-2.37 (m, 3H), 2.22-2.17 (m, 2H), 2.03-2.00 (m, 1H), 1.55-1.52 (m, 2H); MS (ESI) m/z : 520.3 $[\text{M}+\text{H}]^+$.

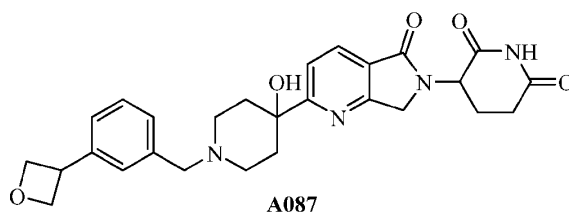


[0484] 3-(2-(4-Hydroxy-1-((3-morpholinophenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A086**. ^1H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.17 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 6.90 (s, 1H), 6.83-6.79 (m, 2H), 5.33-5.23 (m, 1H), 5.19-5.14 (m, 1H), 4.50 (d, J = 17.8 Hz, 1H), 4.33 (d, J =

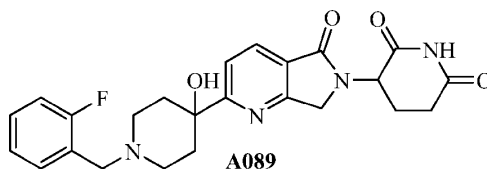
17.6 Hz, 1H), 3.74-3.72 (m, 4H), 3.49 (s, 2H), 3.10-3.08 (m, 4H), 2.96-2.87 (m, 1H), 2.68-2.58 (m, 3H), 2.45-2.37 (m, 3H), 2.24-2.18 (m, 2H), 2.04-1.99 (m, 1H), 1.58-1.52 (m, 2H); MS (ESI) m/z : 520.3 $[M+H]^+$.



[0485] 3-(2-(4-Hydroxy-1-((3-(oxetan-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo-[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A087**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.01 (s, 1H), 8.33 (s, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.34-7.22 (m, 4H), 5.30-5.24 (m, 1H), 5.18-5.14 (m, 1H), 4.96-4.92 (m, 2H), 4.61 (t, $J = 6.4$ Hz, 2H), 4.52-4.48 (m, 1H), 4.34-4.30 (m, 1H), 4.28-4.23 (m, 1H), 3.52 (s, 2H), 2.96-2.87 (m, 1H), 2.66-2.58 (m, 3H), 2.44-2.38 (m, 3H), 2.24-2.18 (m, 2H), 2.04-2.00 (m, 1H), 1.56-1.52 (m, 2H); MS (ESI) m/z : 491.2 $[M+H]^+$.

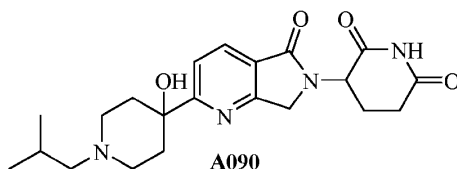


[0486] 3-(2-(1-((2-Fluorophenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A089**. ^1H NMR (400 MHz, DMSO- d_6) δ 10.9 (s, 1H), 8.15-8.11 (m, 2H), 8.23 (d, $J = 8.4$ Hz, 1H), 7.47-7.43 (m, 1H), 7.34-7.29 (m, 1H), 7.20-7.17 (m, 2H), 5.27-5.25 (m, 1H), 5.22-5.13 (m, 1H), 4.49 (d, $J = 17.6$ Hz, 1H), 4.31 (d, $J = 17.6$ Hz, 1H), 3.58 (s, 2H), 2.95-2.88 (m, 1H), 2.68-2.58 (m, 3H), 2.46-2.42 (m, 3H), 2.23-2.18 (m, 2H), 2.03-2.00 (m, 1H), 1.56-1.52 (s, 2H); MS (ESI) m/z : 453.2 $[M+H]^+$.

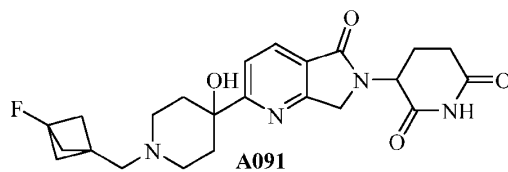


[0487] 3-(2-(4-Hydroxy-1-isobutyl-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)-piperidine-2,6-dione **A090**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.17 (s, 1H), 8.12 (d,

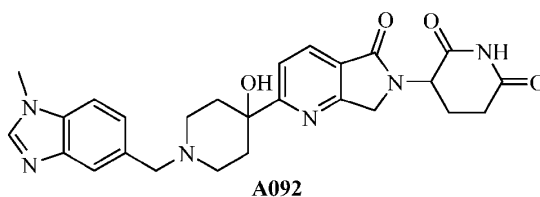
$J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 5.28-5.23 (m, 1H), 5.18-5.14 (m, 1H), 4.50 (d, $J = 17.6$ Hz, 1H), 4.33 (d, $J = 17.6$ Hz, 1H), 2.96-2.88 (m, 1H), 2.69-2.58 (m, 3H), 2.45-2.32 (m, 3H), 2.25-2.19 (m, 2H), 2.12 (d, $J = 7.2$ Hz, 2H), 2.04-2.00 (m, 1H), 1.83-1.77 (m, 1H), 1.56-1.52 (m, 2H), 0.88 (d, $J = 6.8$ Hz, 6H); MS (ESI) m/z : 401.3 $[M+H]^+$.



[0488] 3-(2-(1-((3-Fluorobicyclo[1.1.1]pentan-1-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A091**. ^1H NMR (400 MHz, DMSO- d_6) δ 8.26 (s, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 5.20-5.14 (m, 1H), 4.53-4.29 (m, 2H), 2.97-2.87 (m, 1H), 2.70-2.57 (m, 5H), 2.48-2.38 (m, 3H), 2.25-2.15 (m, 2H), 2.06-2.01 (m, 1H), 1.99 (d, $J = 2.4$ Hz, 6H), 1.55-1.48 (m, 2H); MS (ESI) m/z : 443.2 $[M+H]^+$.

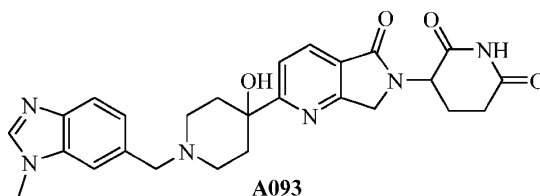


[0489] 3-(2-(4-Hydroxy-1-((1-methylbenzimidazol-5-yl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A092**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.17 (s, 1H), 8.14-8.11 (m, 2H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.57 (s, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.28 (d, $J = 8.4$ Hz, 1H), 5.29-5.27 (m, 1H), 5.19-5.14 (m, 1H), 4.49 (d, $J = 17.6$ Hz, 1H), 4.33 (d, $J = 17.6$ Hz, 1H), 3.82 (s, 3H), 3.65 (s, 2H), 2.93-2.87 (m, 1H), 2.70-2.58 (m, 3H), 2.45-2.41 (m, 3H), 2.25-2.18 (m, 2H), 2.05-2.00 (m, 1H), 1.56-1.52 (m, 2H); MS (ESI) m/z : 489.1 $[M+H]^+$.

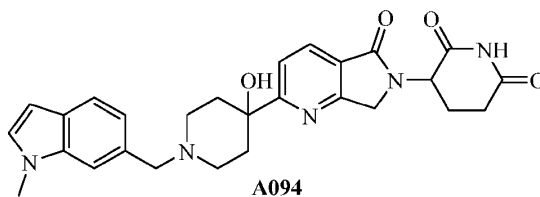


[0490] 3-(2-(4-Hydroxy-1-((3-methylbenzimidazol-5-yl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A093**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.13 (t, $J = 4.0$ Hz, 2H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.60-7.55 (m, 1H), 7.50 (s, 1H), 7.21

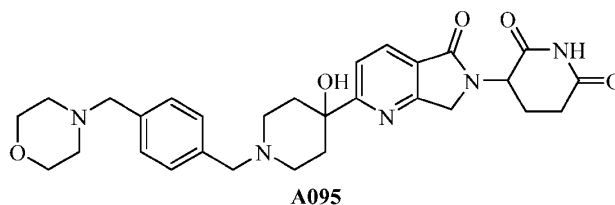
(d, $J = 7.4$ Hz, 1H), 5.27 (s, 1H), 5.17-5.14 (m, 1H), 4.50 (d, $J = 17.8$ Hz, 1H), 4.34-4.30 (m, 1H), 3.83 (s, 3H), 3.64 (s, 2H), 2.96-2.87 (m, 1H), 2.71-2.62 (m, 3H), 2.54 (s, 1H), 2.45-2.41 (m, 2H), 2.26-2.20 (m, 2H), 2.03-1.99 (m, 1H), 1.56-1.52 (m, 2H); MS (ESI) m/z : 489.1 $[M+H]^+$.



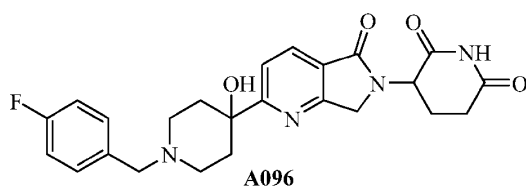
[0491] 3-(2-(4-Hydroxy-1-((1-methylindol-6-yl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A094**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.35 (s, 1H), 7.27 (d, $J = 3.0$ Hz, 1H), 7.03-7.01 (m, 1H), 6.37 (d, $J = 2.6$ Hz, 1H), 5.25 (s, 1H), 5.18-5.14 (m, 1H), 4.52-4.47 (m, 1H), 4.33 (d, $J = 17.6$ Hz, 1H), 3.78 (s, 3H), 3.61 (s, 2H), 2.96-2.87 (m, 1H), 2.70-2.58 (m, 3H), 2.45-2.39 (m, 3H), 2.25-2.18 (m, 2H), 2.05-1.98 (m, 1H), 1.55-1.51 (m, 2H); MS (ESI) m/z : 488.3 $[M+H]^+$.



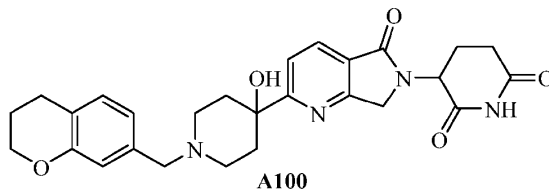
[0492] 3-(2-(4-Hydroxy-1-((4-(morpholinomethyl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A095**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.02-10.97 (m, 1H), 8.21 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.29-7.23 (m, 4H), 5.25 (s, 1H), 5.18-5.14 (m, 1H), 4.51-4.47 (m, 1H), 4.34-4.30 (m, 1H), 3.57-3.54 (m, 4H), 3.49 (s, 2H), 3.43 (s, 2H), 2.97-2.87 (m, 1H), 2.66-2.58 (m, 3H), 2.45-2.33 (m, 7H), 2.25-2.18 (m, 2H), 2.04-2.01 (m, 1H), 1.54-1.51 (m, 2H); MS (ESI) m/z : 534.2 $[M+H]^+$.



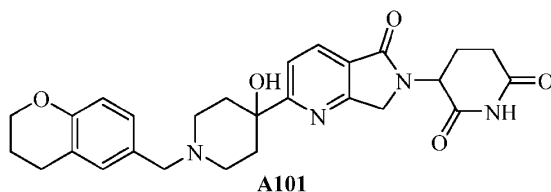
[0493] 3-(2-(1-((4-Fluorophenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]-pyridin-6-yl)piperidine-2,6-dione **A096**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.00 (s, 1H), 8.15 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.39-7.35 (m, 2H), 7.14 (t, *J* = 8.8 Hz, 2H), 5.34-5.27 (m, 1H), 5.18-5.14 (m, 1H), 4.52-4.47 (m, 1H), 4.34-4.30 (m, 1H), 3.51 (s, 2H), 2.95-2.89 (m, 1H), 2.66-2.58 (m, 3H), 2.45-2.39 (m, 3H), 2.24-2.18 (m, 2H), 2.05-2.00 (m, 1H), 1.56-1.52 (m, 2H); MS (ESI) *m/z*: 453.1 [M+H]⁺.



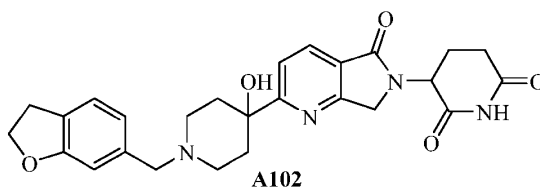
[0494] 3-(2-(1-(Chroman-7-ylmethyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]-pyridin-6-yl)piperidine-2,6-dione **A100**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.78-6.74 (m, 1H), 6.68 (s, 1H), 5.24 (s, 1H), 5.18-5.14 (m, 1H), 4.50 (d, *J* = 17.6 Hz, 1H), 4.34-4.30 (m, 1H), 4.11-4.09 (m, 2H), 3.40 (s, 2H), 2.96-2.87 (m, 1H), 2.71-2.68 (m, 2H), 2.63-2.59 (m, 3H), 2.45-2.35 (m, 3H), 2.25-2.16 (m, 2H), 2.04-1.99 (m, 1H), 1.92-1.86 (m, 2H), 1.54-1.51 (m, 2H); MS (ESI) *m/z*: 491.4 [M+H]⁺.



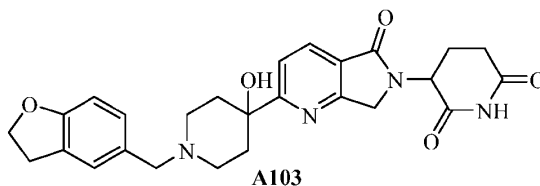
[0495] 3-(2-(1-(Chroman-6-ylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A101**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.13-8.11 (m, 1H), 7.84-7.82 (m, 1H), 7.70-6.98 (m, 2H), 6.67-6.64 (m, 1H), 5.24 (s, 1H), 5.18-5.14 (m, 1H), 4.51-4.47 (m, 1H), 4.35-4.30 (m, 1H), 4.11-4.08 (m, 2H), 3.37 (s, 2H), 2.96-2.87 (m, 1H), 2.74-2.71 (m, 2H), 2.66-2.58 (m, 3H), 2.45-2.33 (m, 3H), 2.21-2.15 (m, 2H), 2.03-2.00 (m, 1H), 1.92-1.87 (m, 1H), 1.58-1.54 (m, 2H); MS (ESI) *m/z*: 491.3 [M+H]⁺.



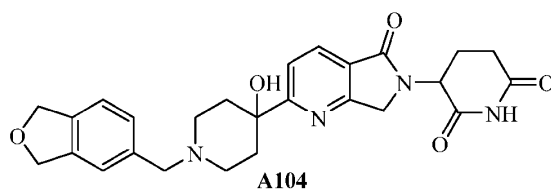
[0496] 3-(2-(1-((2,3-Dihydrobenzofuran-6-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A102**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.13-8.11 (m, 1H), 7.84-7.82 (m, 1H), 7.15-7.13 (m, 1H), 6.79-6.77 (m, 1H), 6.72 (s, 1H), 5.24 (s, 1H), 5.19-5.14 (m, 1H), 4.52-4.48 (m, 3H), 4.34-4.30 (m, 1H), 3.43 (s, 2H), 3.15-3.11 (m, 2H), 2.96-2.87 (m, 1H), 2.62-2.58 (m, 3H), 2.45-2.35 (m, 3H), 2.23-2.11 (m, 2H), 2.04-1.99 (m, 1H), 1.55-1.51 (m, 2H); MS (ESI) m/z : 472.3 $[\text{M}+\text{H}]^+$.



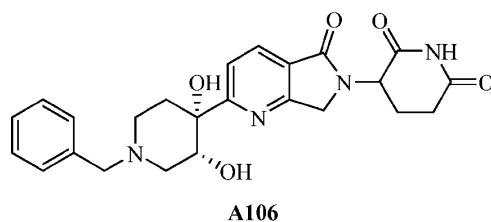
[0497] 3-(2-(1-(2,3-Dihydrobenzofuran-5-yl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A103**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.18 (s, 1H), 7.01 (d, $J = 8.0$ Hz, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 5.24-5.14 (m, 2H), 4.51-4.47 (m, 3H), 4.32 (d, $J = 17.6$ Hz, 1H), 3.41 (s, 2H), 3.17-3.13 (m, 2H), 2.96-2.87 (m, 1H), 2.65-2.58 (m, 3H), 2.45-2.34 (m, 3H), 2.22-2.16 (m, 2H), 2.04-2.00 (m, 1H), 1.54-1.50 (m, 2H); MS (ESI) m/z : 472.2 $[\text{M}+\text{H}]^+$.



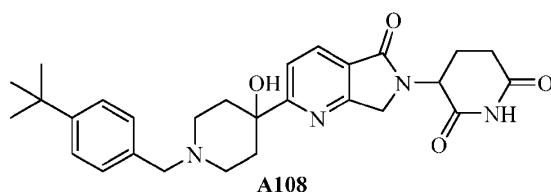
[0498] 3-(2-(1-(1,3-Dihydroisobenzofuran-5-yl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A104**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.00 (s, 1H), 8.17 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.28-7.22 (m, 3H), 5.27 (s, 1H), 5.18-5.14 (m, 1H), 4.98 (d, $J = 3.6$ Hz, 4H), 4.51-4.47 (m, 1H), 4.34-4.30 (m, 1H), 3.53 (s, 2H), 2.98-2.87 (m, 1H), 2.67-2.58 (m, 3H), 2.45-2.39 (m, 3H), 2.24-2.18 (m, 2H), 2.07-2.00 (m, 1H), 1.55-1.51 (m, 2H); MS (ESI) m/z : 472.3 $[\text{M}+\text{H}]^+$.



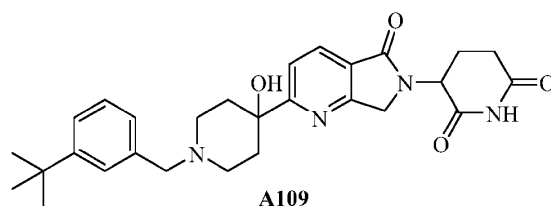
[0499] 3-(2-((3*R*,4*R*)-1-Benzyl-3,4-dihydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A106**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.00 (s, 1H), 8.18 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.34-7.31 (m, 4H), 7.28-7.24 (m, 1H), 5.20-5.13 (m, 1H), 5.02-5.00 (m, 1H), 4.59-4.46 (m, 2H), 4.37-4.28 (m, 1H), 4.11-4.05 (m, 1H), 3.56-3.55 (m, 1H), 3.50 (s, 1H), 2.97-2.87 (m, 1H), 2.70-2.63 (m, 2H), 2.59-2.58 (m, 1H), 2.44-2.31 (m, 2H), 2.24-2.18 (m, 2H), 2.05-2.00 (m, 1H), 1.56-1.51 (m, 1H); MS (ESI) *m/z*: 451.1 [M+H]⁺.



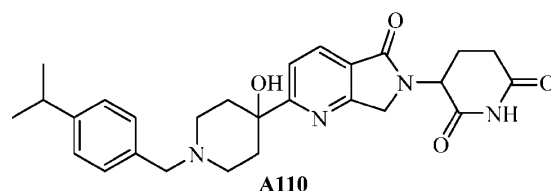
[0500] 3-(2-(1-((4-*Tert*-butylphenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A108**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.18 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.35-7.33 (m, 2H), 7.26-7.24 (m, 2H), 5.38-5.14 (m, 2H), 4.50 (d, *J* = 17.6 Hz, 1H), 4.34-4.30 (m, 1H), 3.50 (s, 2H), 2.95-2.87 (m, 1H), 2.68-2.58 (m, 3H), 2.45-2.40 (m, 3H), 2.24-2.18 (m, 2H), 2.04-1.99 (m, 1H), 1.56-1.52 (m, 2H), 1.27 (s, 9H); MS (ESI) *m/z*: 491.3 [M+H]⁺.



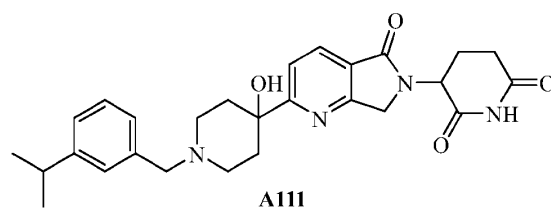
[0501] 3-(2-(1-((3-*Tert*-butylphenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A109**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.19 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.35 (s, 1H), 7.29-7.23 (m, 2H), 7.16 (d, *J* = 6.8 Hz, 1H), 5.19-5.14 (m, 1H), 4.51 (d, *J* = 17.8 Hz, 1H), 4.33 (d, *J* = 17.8 Hz, 1H), 3.57 (s, 2H), 2.96-2.87 (m, 1H), 2.71-2.59 (m, 3H), 2.47-2.37 (m, 3H), 2.26-2.19 (m, 2H), 2.04-2.01 (m, 1H), 1.58-1.54 (m, 2H), 1.28 (s, 9H); MS (ESI) *m/z*: 491.4 [M+H]⁺.



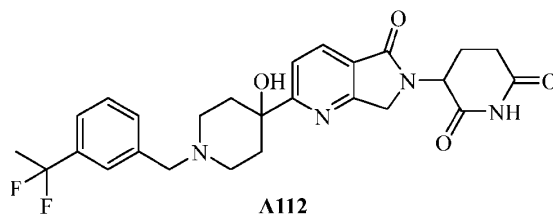
[0502] 3-(2-(4-Hydroxy-1-((4-isopropylphenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]-pyridin-6-yl)piperidine-2,6-dione **A110**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.01 (s, 1H), 8.16 (s, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.26-7.18 (m, 4H), 5.31-5.28 (m, 1H), 5.19-5.14 (m, 1H), 4.52-4.47 (m, 1H), 4.34-4.30 (m, 1H), 3.51 (s, 2H), 2.96-2.84 (m, 2H), 2.68-2.58 (m, 3H), 2.46-2.38 (m, 3H), 2.24-2.16 (m, 2H), 2.04-2.00 (m, 1H), 1.56-1.53 (m, 2H), 1.19 (d, $J = 7.2$ Hz, 6H); MS (ESI) m/z : 477.2 $[\text{M}+\text{H}]^+$.



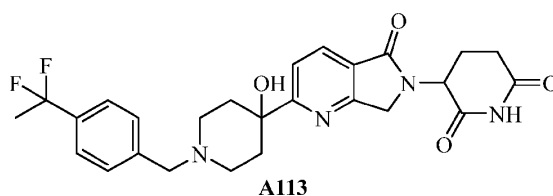
[0503] 3-(2-(4-Hydroxy-1-((3-isopropylphenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]-pyridin-6-yl)piperidine-2,6-dione **A111**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.01 (s, 1H), 8.16 (s, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.26-7.11 (m, 4H), 5.40-5.28 (m, 1H), 5.19-5.14 (m, 1H), 4.55-4.48 (m, 1H), 4.35-4.28 (m, 1H), 3.53 (s, 2H), 2.95-2.84 (m, 2H), 2.69-2.58 (m, 3H), 2.45-2.42 (m, 3H), 2.25-2.19 (m, 2H), 2.04-2.01 (m, 1H), 1.57-1.53 (m, 2H), 1.20 (d, $J = 7.2$ Hz, 6H); MS (ESI) m/z : 477.2 $[\text{M}+\text{H}]^+$.



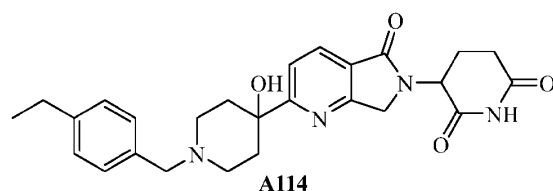
[0504] 3-(2-(1-((3-(1,1-Difluoroethyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A112**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.02 (s, 1H), 8.17-8.12 (m, 2H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.52-7.44 (m, 4H), 5.36-5.29 (m, 1H), 5.19-5.15 (m, 1H), 4.53-4.31 (m, 2H), 3.60 (s, 2H), 2.97-2.88 (m, 1H), 2.68-2.59 (m, 3H), 2.47-2.39 (m, 3H), 2.28-2.20 (m, 2H), 2.05-1.93 (m, 4H), 1.58-1.54 (s, 2H); MS (ESI) m/z : 499.2 $[\text{M}+\text{H}]^+$.



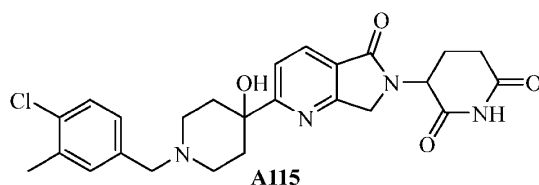
[0505] 3-(2-(1-((4-(1,1-Difluoroethyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A113**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.02 (s, 1H), 8.17-8.12 (m, 2H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.54-7.45 (m, 4H), 5.36-5.27 (m, 1H), 5.19-5.15 (m, 1H), 4.53-4.31 (m, 2H), 3.58 (s, 2H), 2.97-2.88 (m, 1H), 2.68-2.59 (m, 3H), 2.47-2.39 (m, 3H), 2.27-2.20 (m, 2H), 2.05-1.92 (m, 4H), 1.57-1.53 (s, 2H); MS (ESI) m/z : 499.2 $[\text{M}+\text{H}]^+$.



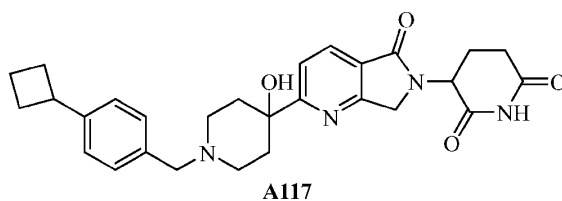
[0506] 3-(2-(1-(4-Ethylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A114**. ^1H NMR (400 MHz, DMSO- d_6) 11.0 (s, 1H), 8.17 (s, 1H), 8.13-8.11 (m, 1H), 7.84-7.82 (m, 1H), 7.25-7.23 (m, 2H), 7.17-7.15 (m, 2H), 5.41-5.14 (m, 2H), 4.52-4.30 (m, 2H), 3.51 (s, 2H), 2.89-2.88 (m, 1H), 2.68-2.59 (m, 5H), 2.46-2.41 (m, 3H), 2.25-2.18 (m, 2H), 2.04-1.99 (m, 1H), 1.56-1.52 (m, 2H), 1.19-1.15 (m, 3H); MS (ESI) m/z : 463.3 $[\text{M}+\text{H}]^+$.



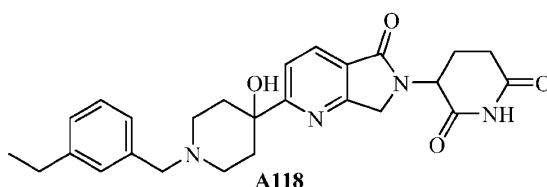
[0507] 3-(2-(1-(4-Chloro-3-methylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A115**. ^1H NMR (400 MHz, DMSO- d_6) δ 11.0 (s, 1H), 8.17 (s, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.31 (s, 1H), 7.20-7.17 (m, 1H), 5.32-5.22 (m, 1H), 5.19-5.14 (m, 1H), 4.53-4.30 (m, 2H), 3.47 (s, 2H), 2.97-2.87 (m, 1H), 2.67-2.63 (m, 3H), 2.41 (t, $J = 10.0$ Hz, 3H), 2.32 (s, 3H), 2.26-2.18 (m, 2H), 2.05-2.00 (m, 1H), 1.56-1.51 (m, 2H); MS (ESI) m/z : 483.1 $[\text{M}+\text{H}]^+$.



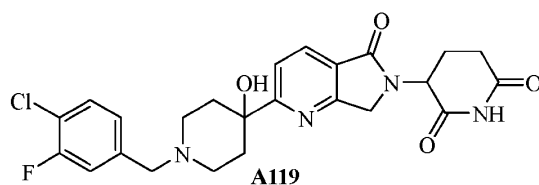
[0508] 3-(2-(1-(4-Cyclobutylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A117**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.0 (s, 1H), 8.16 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 8.83 (d, $J = 8.0$ Hz, 1H), 7.25 (d, $J = 8.0$ Hz, 2H), 7.17 (d, $J = 8.0$ Hz, 2H), 5.26 (s, 1H), 5.18-5.14 (m, 1H), 4.52-4.30 (m, 2H), 3.51-3.48 (m, 2H), 3.47 (s, 2H), 2.93-2.95 (m, 1H), 2.65-2.53 (m, 3H), 2.49-2.40 (m, 3H), 2.38-2.25 (m, 4H), 2.15-1.90 (m, 4H), 1.85-1.65 (m, 1H), 1.55-1.50 (m, 1H); MS (ESI) m/z : 489.3 $[\text{M}+\text{H}]^+$.



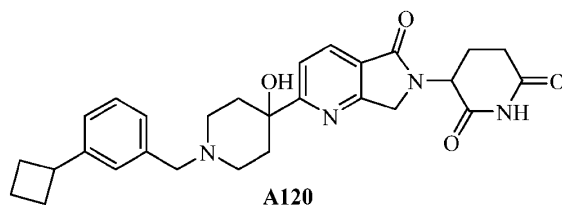
[0509] 3-(2-(1-(3-Ethylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A118**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.0 (s, 1H), 8.23-8.08 (m, 2H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.28-7.05 (m, 4H), 5.36-5.25 (m, 1H), 5.17 (m, 1H), 4.56-4.26 (m, 2H), 3.51 (s, 2H), 2.97-2.88 (m, 1H), 2.68-2.57 (m, 5H), 2.47-2.39 (m, 3H), 2.28-2.17 (m, 2H), 2.07-1.97 (m, 1H), 1.55 (m, 2H), 1.18 (m, 3H); MS (ESI) m/z : 463.1 $[\text{M}+\text{H}]^+$.



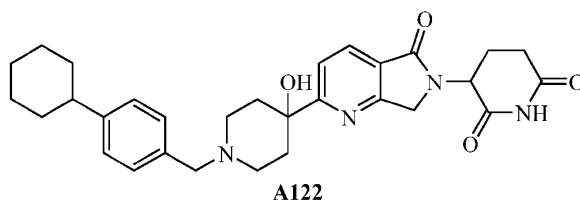
[0510] 3-(2-(1-(4-Chloro-3-fluorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A119**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.0 (s, 1H), 8.18-8.10 (m, 2H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.53 (t, $J = 8.0$ Hz, 1H), 7.37 (d, $J = 9.6$ Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 1H), 5.29 (s, 1H), 5.17 (m, 1H), 4.55-4.27 (m, 2H), 3.53 (s, 2H), 2.96-2.86 (m, 1H), 2.63 (s, 3H), 2.45-2.37 (m, 3H), 2.27-2.17 (m, 2H), 2.07-1.98 (m, 1H), 1.59-1.50 (m, 2H); MS (ESI) m/z : 487.1 $[\text{M}+\text{H}]^+$.



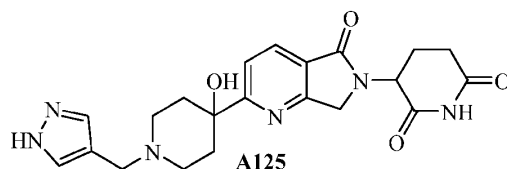
[0511] 3-(2-(1-(3-Cyclobutylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A120**. ^1H NMR (400 MHz, DMSO-*d*₆) δ 11.01 (s, 1H), 8.13-8.11 (m, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.26-7.23 (m, 1H), 7.17- 7.10 (m, 3H), 5.29-5.26 (m, 1H), 5.19-5.14 (m, 1H), 4.52-4.48 (m, 1H), 4.34-4.30 (m, 1H), 3.53-3.50 (m, 2H), 2.96-2.87 (m, 1H), 2.71-2.59 (m, 3H), 2.45-2.42 (m, 3H), 2.32-2.24 (m, 4H), 2.21-1.95 (m, 5H), 1.84-1.79 (m, 1H), 1.56-1.52(m, 2H); MS (ESI) m/z : 489.3 $[\text{M}+\text{H}]^+$.



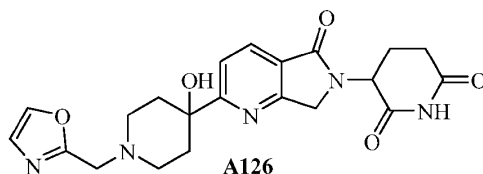
[0512] 3-(2-(1-(4-Cyclohexylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A122**. ^1H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 8.15-8.11 (m, 2H), 7.83 (d, J = 4.0 Hz, 1H), 7.25-7.16 (m, 4H), 5.32-5.29 (m, 1H), 5.27-5.25 (m, 1H) 4.51-4.29 (m, 2H), 3.51 (s, 2H), 2.92-2.88 (m, 1H), 2.69-2.66 (m, 3H), 2.44-2.41 (m, 4H), 2.23-2.16 (m, 2H), 2.08-1.98 (m, 1H), 1.68 (d, J = 8.0 Hz, 4H), 1.56 (d, J = 4.0 Hz, 1H), 1.52 (d, J = 1.6 Hz, 2H), 1.40-1.20 (m, 5H); MS (ESI) m/z : 517.4 $[\text{M}+\text{H}]^+$.



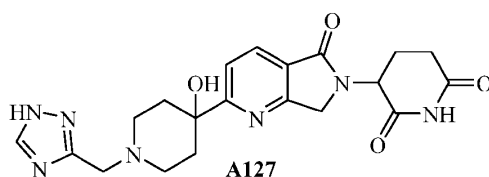
[0513] 3-(2-{4-Hydroxy-1-[(1H-pyrazol-4-yl)methyl]piperidin-4-yl}-5-oxo-5H,6H,7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A125**. MS (ESI) m/z : 425.2 $[\text{M}+\text{H}]^+$.



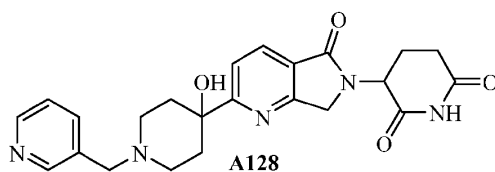
[0514] 3-(2-{4-Hydroxy-1-[(1,3-oxazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A126**. MS (ESI) *m/z*: 426.2 [M+H]⁺.



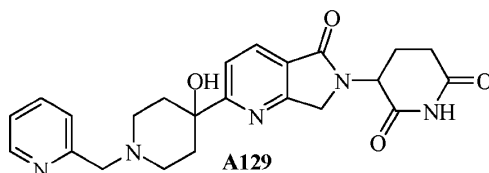
[0515] 3-(2-{4-Hydroxy-1-[(1*H*-1,2,4-triazol-3-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A127**. MS (ESI) *m/z*: 426.2 [M+H]⁺.



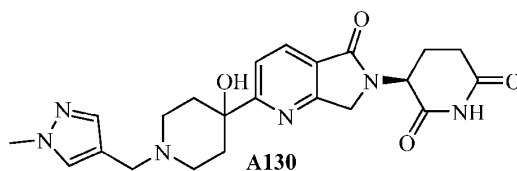
[0516] 3-(2-{4-Hydroxy-1-[(pyridin-3-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A128**. MS (ESI) *m/z*: 436.2 [M+H]⁺.



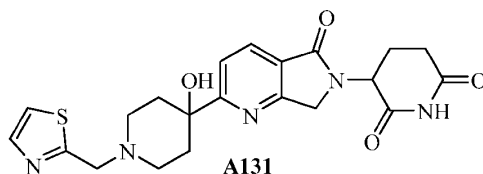
[0517] 3-(2-{4-Hydroxy-1-[(pyridin-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A129**. MS (ESI) *m/z*: 436.2 [M+H]⁺.



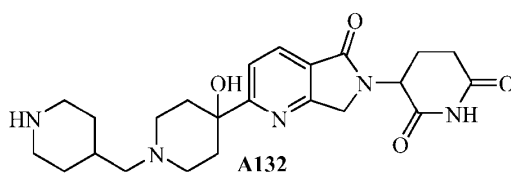
[0518] 3-(2-{4-Hydroxy-1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A130**. MS (ESI) *m/z*: 439.3 [M+H]⁺.



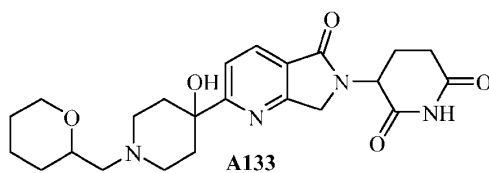
[0519] 3-(2-{4-Hydroxy-1-[(1,3-thiazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A131**. MS (ESI) *m/z*: 442.2 [M+H]⁺.



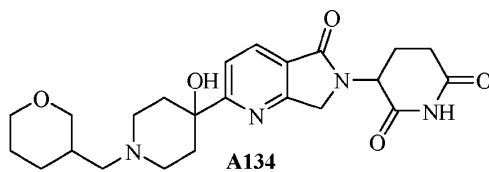
[0520] 3-(2-{4-Hydroxy-1-[(piperidin-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A132**. MS (ESI) *m/z*: 442.3 [M+H]⁺.



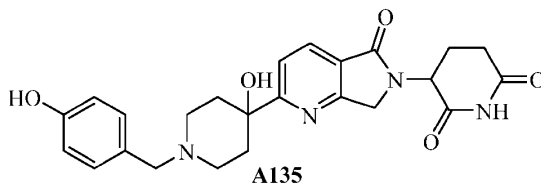
[0521] 3-(2-{4-Hydroxy-1-[(oxan-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A133**. MS (ESI) *m/z*: 443.3 [M+H]⁺.



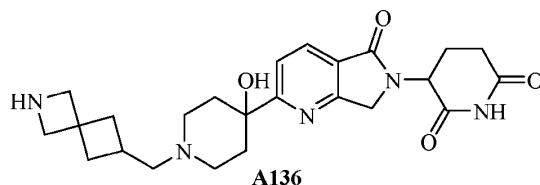
[0522] 3-(2-{4-Hydroxy-1-[(oxan-3-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A134**. MS (ESI) *m/z*: 443.3 [M+H]⁺.



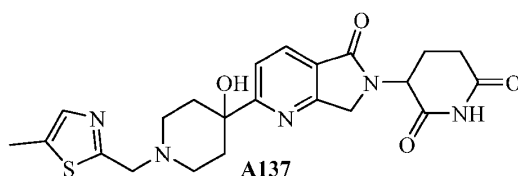
[0523] 3-(2-{4-Hydroxy-1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A135**. MS (ESI) *m/z*: 451.3 [M+H]⁺.



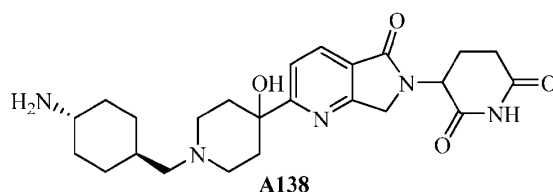
[0524] 3-{2-[1-({2-Azaspiro[3.3]heptan-6-yl)methyl]-4-hydroxypiperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A136**. MS (ESI) *m/z*: 454.3 [M+H]⁺.



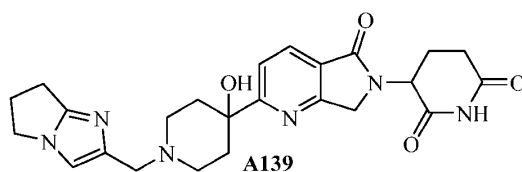
[0525] 3-(2-{4-Hydroxy-1-[(5-methyl-1,3-thiazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A137**. MS (ESI) *m/z*: 456.2 [M+H]⁺.



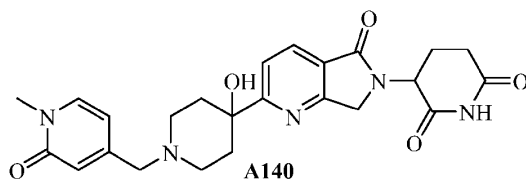
[0526] 3-[2-(4-Hydroxy-1-[(1*r*,4*r*)-4-aminocyclohexyl]methyl]piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A138**. MS (ESI) *m/z*: 456.3 [M+H]⁺.



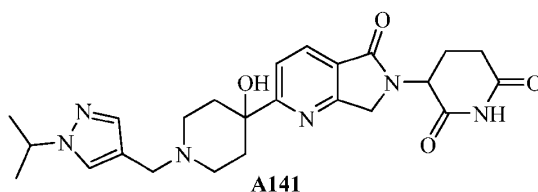
[0527] 3-{2-[4-Hydroxy-1-({5*H*,6*H*,7*H*-pyrrolo[1,2-*a*]imidazol-2-yl)methyl]piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A139**. MS (ESI) *m/z*: 465.3 [M+H]⁺.



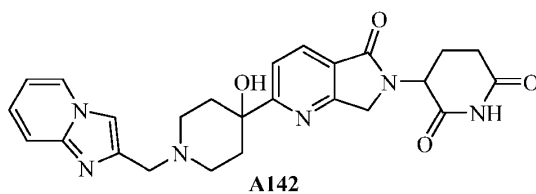
[0528] 3-(2-{4-Hydroxy-1-[(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A140**. MS (ESI) *m/z*: 466.3 [M+H]⁺.



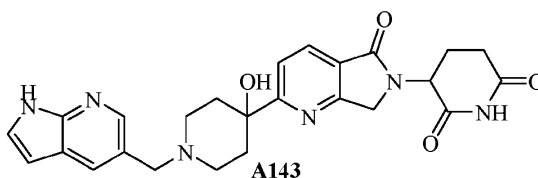
[0529] 3-[2-(4-Hydroxy-1-([1-(propan-2-yl)-1H-pyrazol-4-yl]methyl)piperidin-4-yl)-5-oxo-5H,6H,7H-pyrrolo[3,4-b]pyridin-6-yl]piperidine-2,6-dione **A141**. MS (ESI) m/z : 467.3 $[M+H]^+$.



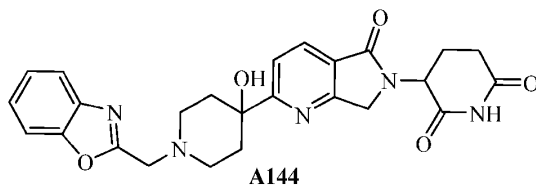
[0530] 3-{2-[4-Hydroxy-1-({imidazo[1,2-*a*]pyridin-2-yl}methyl)piperidin-4-yl]-5-oxo-5H,6H,7H-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A142**. MS (ESI) m/z : 475.2 $[M+H]^+$.



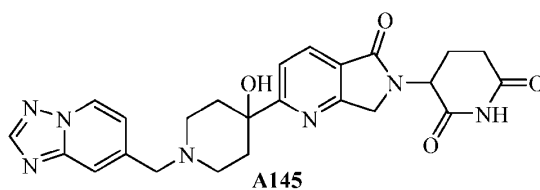
[0531] 3-{2-[4-Hydroxy-1-({1H-pyrrolo[2,3-*b*]pyridin-5-yl}methyl)piperidin-4-yl]-5-oxo-5H,6H,7H-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A143**. MS (ESI) m/z : 475.3 $[M+H]^+$.



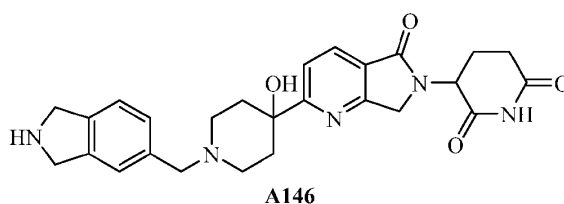
[0532] 3-(2-{1-[(1,3-Benzoxazol-2-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5H,6H,7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A144**. MS (ESI) m/z : 476.2 $[M+H]^+$.



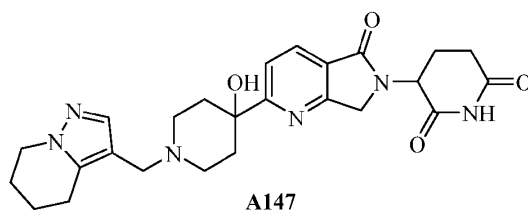
[0533] 3-{2-[4-Hydroxy-1-([1,2,4]triazolo[1,5-*a*]pyridin-7-yl)methyl)piperidin-4-yl]-5-oxo-5H,6H,7H-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A145**. MS (ESI) m/z : 476.3 $[M+H]^+$.



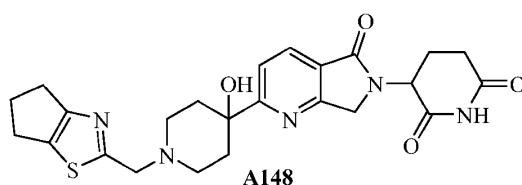
[0534] 3-(2-{1-[(2,3-Dihydro-1*H*-isoindol-5-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A146**. MS (ESI) *m/z*: 476.3 [M+H]⁺.



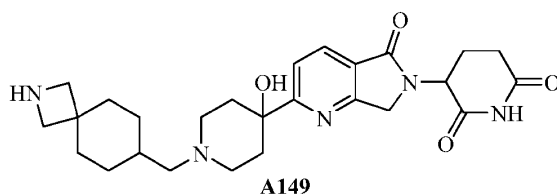
[0535] 3-{2-[4-Hydroxy-1-({4*H*,5*H*,6*H*,7*H*-pyrazolo[1,5-*a*]pyridin-3-yl)methyl]-piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A147**. MS (ESI) *m/z*: 479.3 [M+H]⁺.



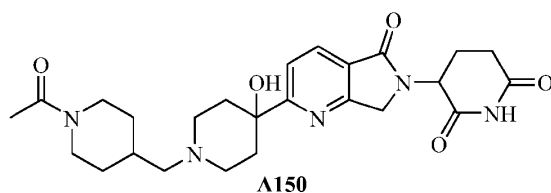
[0536] 3-{2-[1-({4*H*,5*H*,6*H*-Cyclopenta[*d*][1,3]thiazol-2-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A148**. MS (ESI) *m/z*: 482.2 [M+H]⁺.



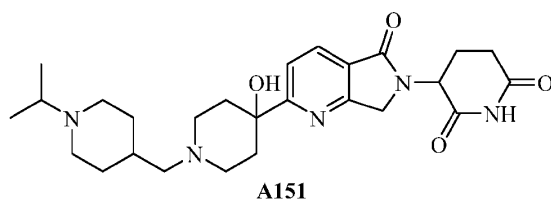
[0537] 3-{2-[1-({2-Azaspiro[3.5]nonan-7-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A149**. MS (ESI) *m/z*: 482.5 [M+H]⁺.



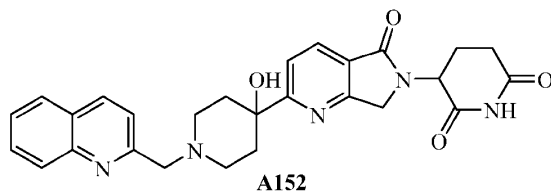
[0538] 3-(2-{1-[(1-Acetylpiperidin-4-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A150**. MS (ESI) m/z : 484.3 $[M+H]^+$.



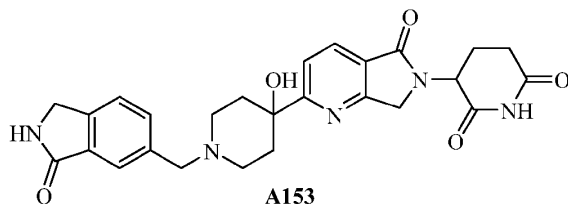
[0539] 3-[2-(4-Hydroxy-1-{[1-(propan-2-yl)piperidin-4-yl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A151**. MS (ESI) m/z : 484.1 $[M+H]^+$.



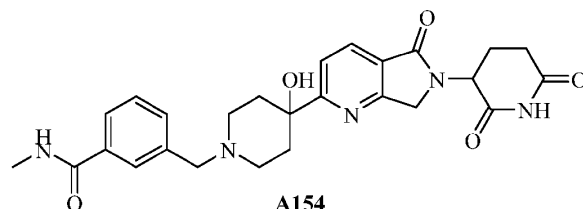
[0540] 3-(2-{4-Hydroxy-1-[(quinolin-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A152**. MS (ESI) m/z : 486.3 $[M+H]^+$.



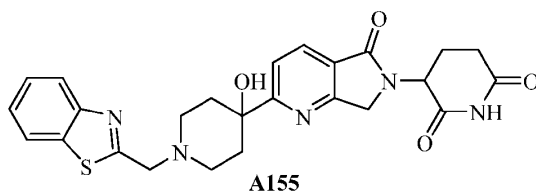
[0541] 3-(2-{4-Hydroxy-1-[(3-oxo-2,3-dihydro-1*H*-isoindol-5-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A153**. MS (ESI) m/z : 490.3 $[M+H]^+$.



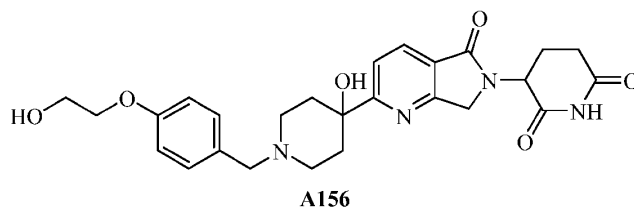
[0542] 3-[(4-{6-[2,6-Dioxopiperidin-3-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-2-yl}-4-hydroxypiperidin-1-yl)methyl]-*N*-methylbenzamide **A154**. MS (ESI) *m/z*: 492.3 [M+H]⁺.



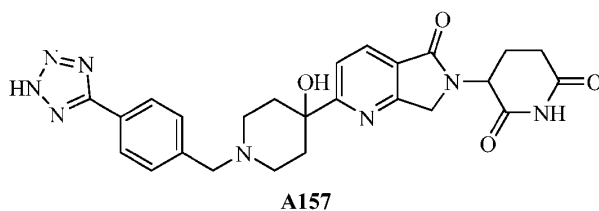
[0543] 3-(2-{1-[(1,3-Benzothiazol-2-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A155**. MS (ESI) *m/z*: 492.2 [M+H]⁺.



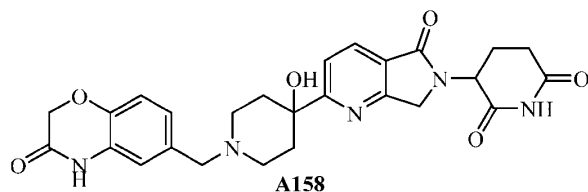
[0544] 3-[2-(4-Hydroxy-1-{[4-(2-hydroxyethoxy)phenyl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A156**. MS (ESI) *m/z*: 495.3 [M+H]⁺.



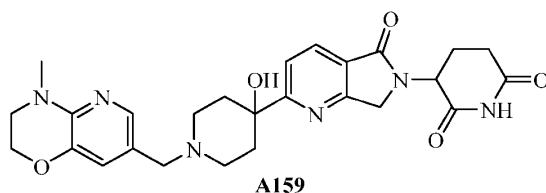
[0545] 3-[2-(4-Hydroxy-1-{[4-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A157**. MS (ESI) *m/z*: 503.3 [M+H]⁺.



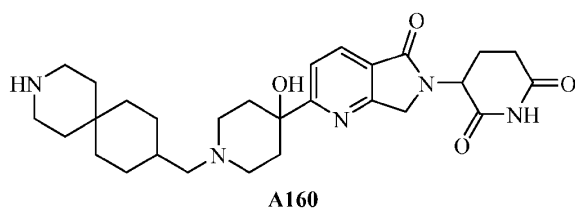
[0546] 3-(2-{4-Hydroxy-1-[(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)methyl]-piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A158**. MS (ESI) *m/z*: 506.3 [M+H]⁺.



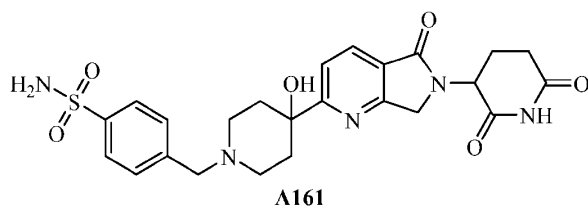
[0547] 3-{2-[4-Hydroxy-1-({4-methyl-2*H*,3*H*,4*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)methyl]-piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A159**. MS (ESI) m/z : 507.3 [M+H]⁺.



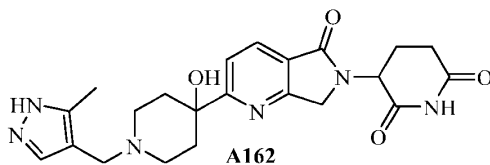
[0548] 3-{2-[1-({3-Azaspiro[5.5]undecan-9-yl)methyl]-4-hydroxypiperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A160**. MS (ESI) m/z : 510.4 [M+H]⁺.



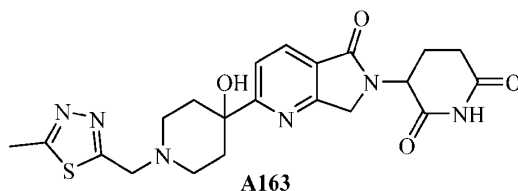
[0549] 4-[(4-{6-[2,6-Dioxopiperidin-3-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-2-yl}-4-hydroxypiperidin-1-yl)methyl]benzene-1-sulfonamide **A161**. MS (ESI) m/z : 514.2 [M+H]⁺.



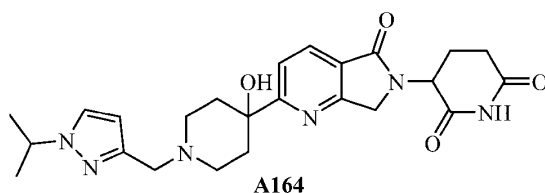
[0550] 3-(2-{4-Hydroxy-1-[(5-methyl-1*H*-pyrazol-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A162**. MS (ESI) m/z : 439.3 [M+H]⁺.



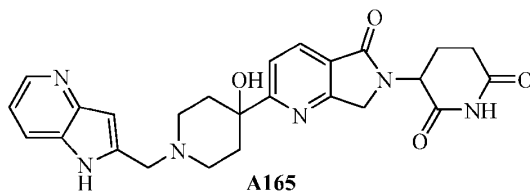
[0551] 3-(2-{4-Hydroxy-1-[(5-methyl-1,3,4-thiadiazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A163**. MS (ESI) *m/z*: 457.2 [M+H]⁺.



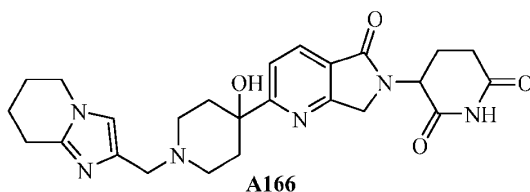
[0552] 3-[2-(4-Hydroxy-1-{[1-(propan-2-yl)-1*H*-pyrazol-3-yl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A164**. MS (ESI) *m/z*: 467.3 [M+H]⁺.



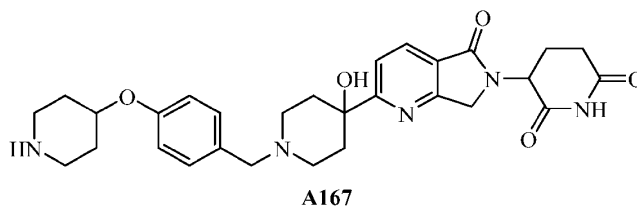
[0553] 3-{2-[4-Hydroxy-1-({1*H*-pyrrolo[3,2-*b*]pyridin-2-yl}methyl)piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A165**. MS (ESI) *m/z*: 475.2 [M+H]⁺.



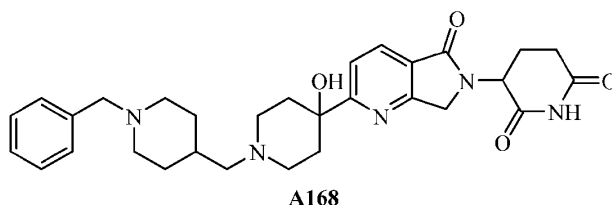
[0554] 3-{2-[4-Hydroxy-1-({5*H*,6*H*,7*H*,8*H*-imidazo[1,2-*a*]pyridin-2-yl}methyl)piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A166**. MS (ESI) *m/z*: 479.3 [M+H]⁺.



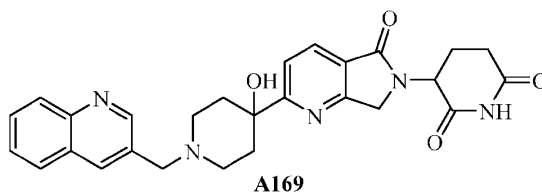
[0555] 3-[2-(4-Hydroxy-1-{[4-(piperidin-4-yloxy)phenyl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A167**. MS (ESI) *m/z*: 534.4 [M+H]⁺.



[0556] 3-(2-{1-[(1-Benzylpiperidin-4-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5H,6H,7H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A168**. MS (ESI) m/z : 532.4 $[M+H]^+$.



[0557] 3-(2-{4-Hydroxy-1-[(quinolin-3-yl)methyl]piperidin-4-yl}-5-oxo-5H,6H,7H-pyrrolo[3,4-b]pyridin-6-yl)piperidine-2,6-dione **A169**. MS (ESI) m/z : 486.3 $[M+H]^+$.



EXAMPLE B1

ARNT and Helios Protein Simple Assay

[0558] Compound dependent degradation of ARNT and helios endogenous proteins was measured using BIO-TECHNE SIMPLE WESTERN immunoassay. NCI-H929 and Jurkat cell lines were used to assay for ARNT and helios, respectively. A compound was dispensed into a 12-well cell culture dish at 0, 0.07, 0.3, 1.2, 4.8, 19, 75, and 300 nM with 0.1% DMSO. The cells were seeded with >90% viability into the wells of the 12-well cell culture dish at 2×10^6 cells/well in a 2 mL final volume. After mixing, the cells were incubated for 6 h at 37 °C in 5% CO₂. The cells were harvested by centrifugation at 3,200 rpm for 2 min and pellets were flash frozen on dry ice. Lysates were prepared by resuspending in a CELL SIGNALING lysis buffer plus inhibitors and allowed to incubate on ice for 45 min. The lysates were cleared by centrifugation at 13,300 rpm for 10 min at 4 °C. Total protein concentration was then determined using a BIO-RAD Bradford protein quantification assay. The JESS fluorescence

separation module protocol was followed using 0.6 mg/mL of NCI-H929 lysates and 0.9 mg/mL of Jurkat lysates. The results for ARNT degradation are shown in FIG. 1 (compound **A001**) and FIG. 2 (3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione). The results for helios degradation are shown in FIG. 5 (compound **A001**) and FIG. 6 (3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione).

EXAMPLE B2

Helios HiBiT Assay in Jurkat Cells

[0559] Compound dependent degradation of helios was measured utilizing Jurkat cells engineered with an endogenously HiBiT-tagged helios protein. A compound was dispensed into a 384-well black clear bottom culture plate. A 10-point dose response was generated in duplicate with a top concentration of 10 μ M and (1:3) dilutions in 0.1% DMSO with a 40 μ L final volume. The compound was evaluated up to 300 nM. The cells were seeded at 40,000 cells/well, centrifuged at 600 rpm for 1 min, and incubated for 24 h at 37 °C in 5% CO₂. The PROMEGA NANO-GLO® HiBiT lytic detection system was employed with addition of a detection reagent (20 μ L/well). After mixing by shaking, the cells were incubated in dark for 20 min at room temperature. The luminescent intensity was then measured using a PERKINELMER ENVISION® multimode plate reader. The results are shown in FIG. 3 (compound **A001**) and FIG. 4 (3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione). [0560] Briefly, compound **A001** degrades ARNT selectively over helios; 3-(5-(1-benzyl-4-hydroxypiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione is much less selective for ARNT over helios. Compound **A001** was determined to have a Y_{min} of 17% for ARNT degradation at 6 h in NCI-H929 cells (FIG. 1) and a Y_{min} of 68% for helios degradation at 6 h in Jurkat cells (FIG. 5). 3-(5-(1-Benzyl-4-hydroxypiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione shows Y_{min} values of 15% for ARNT (FIG. 1) and 26% for helios (FIG. 6) in the same assays.

EXAMPLE B3

VEGF Inhibition Assay in VHL^{mut} 786-O Renal Cell Carcinoma Cells

[0561] The amount of VEGF expression inhibited by disruption of the HIF-2 α /ARNT heterodimer transcription complex was determined by treating VHL mutated cells with compound **A001**, ARNT degrader. The cells were seeded with >90% viability into a 96-well flat

bottom culture plate at 5,000 cells/well in a 200 μ L final volume. The cells were allowed to adhere to the wells by incubating overnight at 37 °C in 5% CO₂. The compound was dispensed at 0, 2.4, 9.8, 39.1, 156.3, 625, 2,500 and 10,000 nM with 0.1% DMSO in duplicate. After mixing by shaking, the cells were incubated for 4 h to allow maximum compound-mediated substrate degradation. Culture media was then removed eliminating excess VEGF, the cells were washed with media, and fresh media was added to the cells. The compound was added back to the wells and allowed to incubate for 20 h. The amount of VEGF secreted into the media was measured using a V-PLEX human VEGF kit (MESO SCALE DIAGNOSTICS). The results are shown in FIG. 7.

EXAMPLE B4

ARNT HiBit Assay in K562 Cells

[0562] K562 cells were engineered to express a HiBiT-tagged endogenous SOS1 ARNT. A compound was dispensed into a 384-well black clear bottom culture microplate. A 10-point dose response was generated for the compound in duplicate with a maximum concentration of 10 μ M and a serial three-fold dilution in 0.1% DMSO with a final volume of 40 μ L. The cells were seeded the 384-well microplate at 40,000 cells/well. After centrifuging at 600 rpm for 1 min, the cells were incubated at 37 °C in 5% CO₂ for 6 h. NANO-GLO® HiBit lytic detection reagent (20 μ L/well) was then added. After shaking for 20 sec, the microplate was incubated in dark at room temperature for 20 min. Luminescent was measured using PERKINELMER ENVISION® multimode plate reader and analyzed to obtain a half-maximal degradation concentration (DC₅₀) and protein remaining (Y_{min}) of the compound. The results are summarized in Table 1, where “A” represents a DC₅₀ of no greater than 1 nM, “B” represents a DC₅₀ of greater than 1 nM and no greater than 10 nM; “C” represents a DC₅₀ of greater than 10 nM and no greater than 100 nM; and “D” represents a DC₅₀ of greater than 100 nM; and where “A” represents a Y_{min} of no greater than 20%, “B” represents a Y_{min} of greater than 20% and no greater than 40%; “C” represents a Y_{min} of greater than 40% and no greater than 60%; and “D” represents a D_{max} of greater than 60%.

TABEL 1. ARNT Protein Degradation

Cmpd.	DC ₅₀	Y _{min}	Cmpd.	DC ₅₀	Y _{min}	Cmpd.	DC ₅₀	Y _{min}
A001	B	A'	A042	C	A'	A083	C	B'
A002	C	A'	A043	C	B'	A084	B	A'
A003	B	C'	A044	C	A'	A085	D	A'
A004	B	A'	A045	B	C'	A086	B	A'
A005	B	B'	A046	D	A'	A087	C	A'
A006	B	B'	A047	C	B'	A088	A	A'
A007	D	B'	A048	B	A'	A089	A	B'
A008	A	B'	A049	C	B'	A090	D	A'
A009	B	A'	A050	C	A'	A091	D	B'
A010	B	B'	A051	D	A'	A092	D	B'
A011	D	A'	A052	D	C'	A093	A	B'
A012	A	A'	A053	B	A'	A094	C	B'
A013	C	C'	A054	B	B'	A095	C	A'
A014	C	A'	A055	C	A'	A096	B	A'
A015	B	A'	A056	A	C'	A097	B	A'
A016	C	A'	A057	B	A'	A098	B	A'
A017	A	A'	A058	C	B'	A099	C	B'
A018	A	A'	A059	A	A'	A100	C	B'
A019	D	B'	A060	C	A'	A101	B	B'
A020	C	B'	A061	D	A'	A102	B	B'
A021	C	B'	A062	C	A'	A103	A	A'
A022	B	C'	A063	B	A'	A104	D	B'
A023	C	C'	A064	C	A'	A105	A	C'
A025	C	A'	A065	A	A'	A106	C	D'
A024	C	A'	A066	A	A'	A107	B	A'
A026	A	A'	A067	B	A'	A108	B	A'
A027	C	B'	A068	B	A'	A109	B	B'
A028	A	B'	A069	C	A'	A110	B	A'
A029	B	B'	A070	B	A'	A111	C	A'
A030	C	B'	A071	D	B'	A112	A	A'
A031	D	A'	A072	C	C'	A113	A	A'
A032	D	C'	A073	C	B'	A114	B	A'
A033	C	B'	A074	B	C'	A115	B	B'
A034	A	A'	A075	D	A'	A116	B	A'
A035	B	C'	A076	D	B'	A117	C	A'
A036	D	B'	A077	A	B'	A118	C	B'
A037	C	B'	A078	C	A'	A119	B	B'

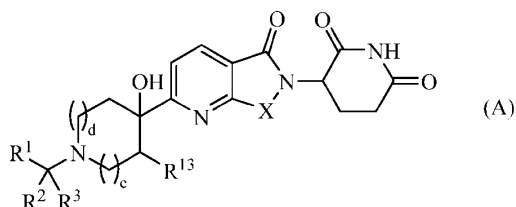
Cmpd.	DC₅₀	Y_{min}	Cmpd.	DC₅₀	Y_{min}	Cmpd.	DC₅₀	Y_{min}
A038	D	B'	A079	C	A'	A120	C	B'
A039	A	A'	A080	C	A'	A121	A	A'
A040	D	A'	A081	B	A'	A122	C	A'
A041	C	B'	A082	C	A'	C001	C	D'

[0563] This disclosure is not to be limited in scope by the embodiments disclosed in the examples which are intended as single illustrations of individual aspects, and any equivalents are within the scope of this disclosure. Various modifications in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

[0564] Various references such as patents, patent applications, and publications are cited herein, the disclosures of which are hereby incorporated by reference herein in their entireties.

What is claimed is:

1. A compound having the structure of Formula (A):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein:

R^1 is C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, C_6 - C_{14} aryl, C_7 - C_{15} arylalkyl, heteroaryl, or heterocycloalkyl;

R^2 and R^3 are each independently H, deuterium, C_1 - C_{10} alkyl, or C_3 - C_{10} cycloalkyl; or R^2 and R^3 together with the carbon atom to which they are attached form $C(O)$ or C_3 - C_{10} cycloalkyl;

R^{13} is H, deuterium, or hydroxyl;

X is CR^4R^5 or $C(O)$, wherein R^4 and R^5 are each independently H, deuterium, or C_1 - C_{10} alkyl; and

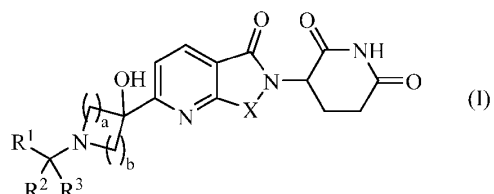
c and d are each independently an integer of 0, 1, or 2;

wherein each alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heterocycloalkyl is optionally substituted with one, two, three, or four substituents, each of which is independently deuterium, cyano, halo, oxo, nitro, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-COR'$, $-CO_2R'$, $-CONR'R''$, $-OR'$, $-OC(O)R'$, $-OC(O)NR'R''$, $-NR'R''$, $-NR''C(O)R'$, $-NR''C(O)_2R'$, $-NR'C(O)NR''R'''$, $-NRSO_2R'$, $-NRSO_2NR'R''$, $-SR'$, $-S(O)R'$, $-S(O)_2R'$, or $-S(O)_2NR'R''$; and

wherein each R' , R'' , and R''' is independently hydrogen, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_1 - C_{10}

cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

2. The compound of claim 1, having the structure of Formula (I):



or a pharmaceutically acceptable derivative thereof, wherein:

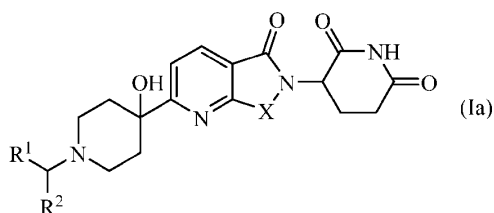
R¹ is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R² and R³ are each independently H, alkyl, or cycloalkyl, or R² and R³ together form spirocycloalkyl;

a and b are each independently an integer from 1 to 3; and

X is CR⁴R⁵ or C(O), where R⁴ and R⁵ are each independently H, alkyl, or aralkyl.

3. The compound of claim 2, having the structure of Formula (Ia):



or a pharmaceutically acceptable derivative thereof, wherein:

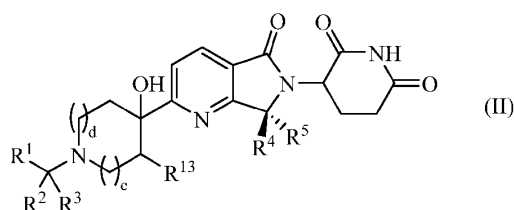
R¹ is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R² is H, alkyl, or cycloalkyl; and

X is CR⁴R⁵ or C(O), where R⁴ and R⁵ are each independently H, alkyl, or aralkyl.

4. The compound of any one of claims 1 to 3, wherein X is CR⁴R⁵.

5. The compound of claim 1 or 4, having the structure of Formula (II):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof.

6. The compound of any one of claims 1 to 5, wherein:

(i) R¹ is aryl or heteroaryl, each optionally substituted with -OR⁶, -NR⁷R⁸, -(CH₂)_n-R⁹, -C(O)NR⁷R⁸, -NR⁷C(O)R¹², -S(O)_pNR⁷R⁸, -NR⁷S(O)_pR¹², -C(O)-(CH₂)_m-R¹⁰, or -S(O)_p-(CH₂)_q-R¹¹, where R⁶ is H, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each R⁷ and R⁸ is independently H, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or R⁷ and R⁸ together with the atom(s) to which they are attached form heterocycloalkyl; R⁹, R¹⁰, and R¹¹ are each independently monocyclic or fused, bridged, or spiro bicyclic cycloalkyl, or monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; R¹² is alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and each m, n, p, and q is independently an integer from 0-2; or

(ii) R¹ is aryl or heteroaryl, each optionally fused to a cycloalkyl or heterocycloalkyl ring.

7. The compound of any one of claims 1 to 6, wherein R¹ is aryl or heteroaryl, each optionally substituted with -OR⁶, -NR⁷R⁸, -(CH₂)_n-R⁹, -C(O)NR⁷R⁸, -NR⁷C(O)R¹², -S(O)_pNR⁷R⁸, -NR⁷S(O)_pR¹², -C(O)-(CH₂)_m-R¹⁰, or -S(O)_p-(CH₂)_q-R¹¹; where R⁶ is H, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each R⁷ and R⁸ is independently H, alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or R⁷ and R⁸ together with the atom(s) to which they are attached form heterocycloalkyl; R⁹, R¹⁰, and R¹¹ are each independently monocyclic or fused, bridged, or spiro bicyclic cycloalkyl, or monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; R¹² is alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and each m, n, p, and q is independently an integer from 0-2.

8. The compound of any one of claims 1 to 7, wherein R^1 is aryl, optionally substituted with $-OR^6$, $-NR^7R^8$, $-(CH_2)_n-R^9$, $-C(O)NR^7R^8$, $-NR^7C(O)R^{12}$, $-S(O)_pNR^7R^8$, $-NR^7S(O)_pR^{12}$, $-C(O)R^{10}$, or $-S(O)_2R^{11}$; where R^6 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each R^7 and R^8 is independently H, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, or R^7 and R^8 together with the atom(s) to which they are attached form heterocycloalkyl; R^9 , R^{10} , and R^{11} are each independently monocyclic or fused, bridged, or spiro bicyclic cycloalkyl or monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; R^{12} is alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and each n and p is independently an integer from 0-2.

9. The compound of any one of claims 1 to 8, wherein R^1 is aryl, optionally substituted with $-OR^6$, $-NR^7R^8$, $-(CH_2)_n-R^9$, $-C(O)NR^7R^8$, $-NR^7C(O)R^{12}$, $-S(O)_pNR^7R^8$, $-NR^7S(O)_pR^{12}$, $-C(O)R^{10}$, or $-S(O)_2R^{11}$; where R^6 is heterocycloalkyl or aryl; R^7 is H; R^8 is heterocycloalkyl or aryl; R^9 , R^{10} , and R^{11} are each independently monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; R^{12} is alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and n is an integer of 0 or 1 and p is an integer from 0-2.

10. The compound of any one of claims 1 to 9, wherein R^1 is aryl, optionally substituted with $-OR^6$, $-NR^7R^8$, $-(CH_2)_n-R^9$, $-C(O)R^{10}$, or $-S(O)_2R^{11}$; where R^6 is heterocycloalkyl or aryl; R^7 is H; R^8 is heterocycloalkyl or aryl; R^9 , R^{10} , and R^{11} are each independently monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; and n is an integer of 0 or 1.

11. The compound of any one of claims 1 to 10, wherein R^1 is optionally substituted phenyl.

12. The compound of any one of claims 1 to 9 and 11, wherein R^1 is phenyl, optionally substituted with $-OR^6$, $-NR^7R^8$, $-(CH_2)_n-R^9$, $-C(O)NR^7R^8$, $-NR^7C(O)R^8$, $-C(O)R^{10}$, or $-S(O)_2R^{11}$; where R^6 is heterocycloalkyl or aryl; R^7 is H; R^8 is heterocycloalkyl or aryl; R^9 , R^{10} , and R^{11} are each independently monocyclic or fused, bridged, or spiro bicyclic heterocycloalkyl; and n is an integer of 0 or 1.

13. The compound of any one of claims 1 to 12, wherein R^1 is unsubstituted phenyl.

14. The compound of any one of claims 1 to 6, wherein R¹ is aryl, optionally fused to a cycloalkyl or heterocycloalkyl ring.

15. The compound of any one of claims 1 to 6 and 14, wherein R¹ is phenyl, optionally fused to a heterocycloalkyl ring.

16. The compound of any one of claims 1, 4, and 5, wherein R¹ is C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, C₇-C₁₅ arylalkyl, heteroaryl, or heterocycloalkyl, each optionally substituted one, two, three, or four substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

17. The compound of any one of claims 1, 4, 5, and 16, wherein R¹ is C₁-C₁₀ alkyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

18. The compound of any one of claims 1, 4, 5, 16, and 17, wherein R¹ is isopropyl.

19. The compound of any one of claims 1 to 5 and 16, wherein R¹ is C₃-C₁₀ cycloalkyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

20. The compound of any one of claims 1 to 5, 16, and 19, wherein R¹ is monocyclic or bicyclic C₃-C₁₀ cycloalkyl, each optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, oxo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

21. The compound of any one of claims 1 to 5, 16, 19, and 20, wherein R¹ is cyclohexyl, 4-aminocyclohexyl, or 3-fluorobicyclo[1.1.1]pentan-1-yl.

22. The compound of any one of claims 1 to 5 and 16, wherein R¹ is C₆-C₁₄ aryl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

23. The compound of any one of claims 1 to 5, 16, and 22, wherein R¹ is phenyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

24. The compound of any one of claims 1 to 5, 16, 22, and 23, wherein R¹ is phenyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, or -OR'; wherein R' is substituted or unsubstituted C₁-C₁₀ alkyl, or substituted or unsubstituted C₆-C₁₄ aryl.

25. The compound of any one of claims 1 to 5, 16, 22, and 23, wherein R¹ is phenyl, optionally substituted one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidinyl, difluoropiperidinyl, (hydroxymethyl)piperidinyl, hydroxypiperidinyl, oxanyl, morpholino, 8-azabicyclo[3.2.1]octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyl, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl.

26. The compound of any one of claims 1 to 5, 16, and 22 to 25, wherein R¹ is phenyl, optionally substituted one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, morpholinomethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazolyl, methylpyrazolyl, piperidinyl, morpholino, 8-azabicyclo[3.2.1]octanyl, or phenoxy.

27. The compound of any one of claims 1 to 5, 16, 22, 23, and 25, wherein R¹ is phenyl, optionally substituted one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yloxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl.

28. The compound of any one of claims 1 to 5, 16, and 22 to 27, wherein R¹ is phenyl, optionally substituted one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, morpholinomethyl, methoxymethyl, phenoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, or phenoxy.

29. The compound of any one of claims 1 to 5, 16, 22, 23, 25, and 27, wherein R¹ is phenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 3-(1,1-difluoroethyl)phenyl, 4-(1,1-difluoroethyl)phenyl, 3-isopropylphenyl, 4-isopropylphenyl, 3-*tert*-butylphenyl, 4-*tert*-butylphenyl, 4-(oxan-4-ylmethyl)phenyl, 4-(morpholinomethyl)phenyl, 4-hydroxymethylphenyl, 4-methoxymethylphenyl, 4-phenoxy-methylphenyl, 4-((dimethylamino)methyl)phenyl, 4-chloro-3-fluorophenyl, 4-chloro-3-methylphenyl, 3,4-di(trifluoromethyl)phenyl, 3-cyclobutylphenyl, 4-cyclobutylphenyl, 4-cyclohexylphenyl, 4-phenylphenyl, 4-pyrazol-1-ylphenyl, 4-(1-methylpyrazol-3-yl)phenyl, 4-(1-methylpyrazol-4-yl)phenyl, 4-(2-methylpyrazol-3-yl)phenyl, 3-(oxetan-3-yl)phenyl, 4-(oxetan-3-yl)-phenyl, 3-oxan-4-ylphenyl, 4-oxan-4-ylphenyl, 3-(piperidin-1-yl)phenyl, 4-(piperidin-1-yl)-phenyl, 4-(4,4-difluoropiperidin-1-yl)phenyl, 4-(4-(hydroxymethyl)piperidin-1-yl)phenyl, 4-(4-hydroxypiperidin-1-yl)phenyl, 3-morpholinophenyl, 4-morpholinophenyl, 3-(8-azabicyclo[3.2.1]octan-8-yl)phenyl, 4-(8-azabicyclo[3.2.1]octan-8-yl)phenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-trifluoromethoxyphenyl, 4-(2-hydroxyethoxy)phenyl, 3-phenoxyphenyl, 4-phenoxyphenyl, 4-benzoxyphe-nyl, 4-(piperidin-4-yloxy)phenyl, 4-(oxan-4-yl)oxyphenyl, 3,4-dimethoxyphenyl, 3-amino-phenyl, 3-dimethylaminophenyl, 4-dimethylaminophenyl, 4-phenylaminophenyl, 3-amino-carbonylphenyl, 4-aminocarbonylphenyl, 3-methylaminocarbonylphenyl, 4-methylamino-carbonylphenyl, 4-dimethylaminocarbonylphenyl, 4-(methylsulfonyl)phenyl, or 4-amino-sulfonylphenyl.

30. The compound of any one of claims 1 to 5, 16, and 22 to 29, wherein R¹ is phenyl, 3-cyanophenyl, 4-cyanophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-methylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-ethylphenyl, 3-(1,1-difluoroethyl)phenyl, 4-(1,1-difluoroethyl)phenyl, 4-isopropylphenyl, 4-*tert*-butylphenyl, 4-(oxan-4-ylmethyl)phenyl, 4-methoxymethylphenyl, 4-phenylphenyl, 4-pyrazol-1-ylphenyl, 4-(1-methylpyrazol-3-yl)phenyl, 4-(1-methylpyrazol-4-yl)phenyl, 4-(piperidin-1-yl)phenyl, 3-morpholinophenyl, 3-(8-azabicyclo[3.2.1]octan-8-yl)phenyl, 4-(8-azabicyclo[3.2.1]octan-8-yl)-phenyl, 3-phenoxyphenyl, or 4-phenoxyphenyl.

31. The compound of any one of claims 1 to 5, 16, and 22, wherein R¹ is bicyclic C₈-C₁₄ aryl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

32. The compound of any one of claims 1, 4, 5, 16, 22, and 31, wherein R¹ is 2,3-dihydroinden-2-yl.

33. The compound of any one of claims 1, 4, 5, and 16, wherein R¹ is C₇-C₁₅ arylalkyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

34. The compound of any one of claims 1, 4, 5, 16, and 33, wherein R¹ is benzyl or 3-fluorobenzyl.

35. The compound of any one of claims 1 to 5 and 16, wherein R¹ is heteroaryl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

36. The compound of any one of claims 1 to 5, 16, and 35, wherein R¹ is substituted or unsubstituted monocyclic heteroaryl.

37. The compound of any one of claims 1 to 5, 16, 35, and 36, wherein R¹ is 5- or 6-membered heteroaryl, each optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

38. The compound of any one of claims 1 to 5, 16, and 35 to 37, wherein R¹ is isoxazolyl, oxazolyl, pyrazolyl, thiazolyl, 1,2,4-triazolyl, 1,3,4-thiadiazolyl, tetrazolyl, or pyridinyl, each optionally substituted one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl.

39. The compound of any one of claims 1 to 5, 16, and 35 to 38, wherein R¹ is isoxazol-4-yl, oxazol-2-yl, pyrazol-3-yl, pyrazol-4-yl, thiazol-2-yl, 1,2,4-triazol-3-yl, 1,3,4-thiadiazol-2-yl, tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, each optionally one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl.

40. The compound of any one of claims 1, 4, 5, 16, and 35 to 39, wherein R¹ is isoxazol-4-yl, oxazol-2-yl, pyrazol-4-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 3-methylpyrazol-4-yl, 1-(trifluoromethyl)pyrazol-4-yl, 1-(isopropyl)pyrazol-3-yl, 1-(isopropyl)pyrazol-4-yl, 1-phenyl-pyrazol-4-yl, thiazol-2-yl, 5-methylthiazol-2-yl, 1,2,4-triazol-3-yl, 5-methyl-1,3,4-thiadiazol-2-yl, tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 2-hydroxypyridin-4-yl, or 1-methyl-2-oxo-1,2-dihydro-pyridin-4-yl.

41. The compound of any one of claims 1 to 5, 16, and 35, wherein R¹ is substituted or unsubstituted bicyclic heteroaryl.

42. The compound of any one of claims 1 to 5, 16, 35, and 41, wherein R¹ is 5,5-, 5,6-, or 6,6-fused heteroaryl, each optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl,

substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R'', -OR', -NR'R'', -S(O)₂R', or -S(O)₂NR'R''.

43. The compound of any one of claims 1 to 5, 16, 35, 41, and 42, wherein R¹ is 5,6-dihydrocyclopenta[*d*]thiazolyl, 6,7-dihydropyrrolo[1,2-*a*]imidazolyl benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzo[*d*][1,2,3]triazolyl, imidazo[1,2-*a*]pyridinyl, indolyl, indazolyl, pyrazolo[1,5-*a*]pyridinyl, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[3,2-*b*]pyridinyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, 2,3-dihydroisindolyl, 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl, benzo[*d*][1,3]dioxolyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridinyl, 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridinyl, quinolinyl, chromanyl, 3,4-dihydropyrido[3,2-*b*][1,4]oxazinyl, or 3,4-dihydro-1,4-benzoxazinyl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl.

44. The compound of any one of claims 1 to 5, 16, 35, and 41 to 43, wherein R¹ is 5,6-dihydrocyclopenta[*d*]thiazol-2-yl, 6,7-dihydropyrrolo[1,2-*a*]imidazol-2-yl, benzofuran-6-yl, benzimidazol-5-yl, benzoxazol-2-yl, benzothiazol-2-yl, benzo[*d*][1,2,3]triazol-5-yl, imidazo[1,2-*a*]pyridin-2-yl, indol-5-yl, indol-6-yl, indazol-4-yl, indazol-5-yl, indazol-6-yl, pyrazolo[1,5-*a*]pyridin-6-yl, pyrrolo[2,3-*b*]pyridin-5-yl, pyrrolo[3,2-*b*]pyridin-2-yl, pyrrolo[3,2-*b*]pyridin-6-yl, [1,2,4]triazolo[1,5-*a*]pyridin-7-yl, 2,3-dihydroisindol-5-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, 1,3-dihydroisobenzofuran-5-yl, benzo[*d*][1,3]dioxol-5-yl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl, 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridin-3-yl, quinolin-2-yl, quinolin-3-yl, quinolin-6-yl, chroman-6-yl, chroman-7-yl, 3,4-dihydropyrido[3,2-*b*][1,4]oxazin-7-yl, or 3,4-dihydro-1,4-benzoxazin-6-yl, each optionally substituted with one or two substituents, each of which is independently deuterium, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, or phenyl.

45. The compound of any one of claims 1 to 5, 16, 35, and 41 to 44, wherein R¹ is 5,6-dihydrocyclopenta[*d*]thiazol-2-yl, 6,7-dihydropyrrolo[1,2-*a*]imidazol-2-yl, benzofuran-6-yl, 1-methylbenzimidazol-5-yl, 3-methylbenzimidazol-5-yl, benzoxazol-2-yl, benzothiazol-2-yl, 1-methylbenzo[*d*][1,2,3]triazol-5-yl, imidazo[1,2-*a*]pyridin-2-yl, 1-methylindol-5-yl, 1-methyl-

indol-6-yl, indazol-5-yl, 1-methylindazol-4-yl, 1-methylindazol-5-yl, 1-methylindazol-6-yl, pyrazolo[1,5-*a*]pyridin-6-yl, 2,2-difluorobenzo[*d*][1,3]dioxol-5-yl, pyrrolo[2,3-*b*]pyridin-5-yl, pyrrolo[3,2-*b*]pyridin-2-yl, pyrrolo[3,2-*b*]pyridin-6-yl, 2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl, 2,2-dimethyl-2,3-dihydrobenzofuran-6-yl, [1,2,4]triazolo[1,5-*a*]pyridin-7-yl, 1,3-dihydroisobenzofuran-5-yl, 2,3-dihydrobenzofuran-5-yl, 3-oxo-3,4-dihydro-1,4-benzoxazin-6-yl, 2,3-dihydroinden-2-yl, 2,3-dihydroisoindol-5-yl, 3-oxo-2,3-dihydroisoindol-5-yl, 2,3-dihydrobenzofuran-6-yl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl, 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridin-3-yl, quinolin-2-yl, quinolin-3-yl, quinolin-6-yl, chroman-6-yl, chroman-7-yl, 4-methyl-3,4-dihydropyrido[3,2-*b*][1,4]oxazin-7-yl, or 3-oxo-3,4-dihydro-1,4-benzoxazin-6-yl.

46. The compound of any one of claims 1 to 5 and 16, wherein R¹ is heterocycloalkyl, optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

47. The compound of any one of claims 1 to 5, 16, and 46, wherein R¹ is substituted or unsubstituted monocyclic heterocycloalkyl.

48. The compound of any one of claims 1 to 5, 16, 46, and 47, wherein R¹ is 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl, each optionally substituted one, two, or three substituents, each of which is independently deuterium, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

49. The compound of any one of claims 1 to 5, 16, and 46 to 48, wherein R¹ is azetidiny, oxany, piperidiny, tetrahydrothiopyrany, 2-azaspiro[3.3]heptany, 2-azaspiro[3.5]nonany, 3-azaspiro[5.5]undecany, or 8-azabicyclo-[3.2.1]octany, each optionally substituted

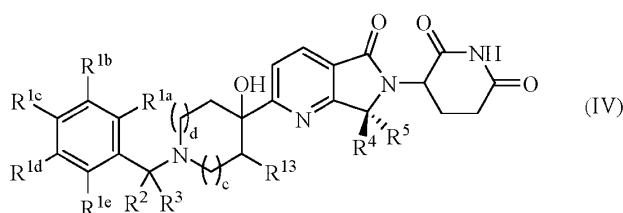
with one or two substituents, each of which is independently oxo, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, phenyl, or pyridinyl.

50. The compound of any one of claims 1 to 5, 16, and 46 to 49, wherein R^1 is azetidin-3-yl, oxan-2-yl, oxan-3-yl, piperidin-3-yl, piperidin-4-yl, tetrahydrothiopyran-4-yl, 2-azaspiro[3.3]heptan-6-yl, 2-azaspiro[3.5]nonan-7-yl, 3-azaspiro[5.5]undecan-9-yl, or 8-azabicyclo[3.2.1]octan-3-yl, each optionally substituted with one or two substituents, each of which is independently oxo, cyano, chloro, fluoro, methyl, trifluoromethyl, isopropyl, phenyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl.

51. The compound of any one of claims 1 to 5, 16, and 46 to 50, wherein R^1 is 1-phenylazetidin-3-yl, oxan-2-yl, oxan-3-yl, piperidin-4-yl, 1-(isopropyl)piperidin-4-yl, 1-phenylpiperidin-3-yl, 1-phenylpiperidin-4-yl, 1-(2-chlorophenyl)piperidin-4-yl, 1-(3-chlorophenyl)piperidin-4-yl, 1-(4-chlorophenyl)piperidin-4-yl, 1-benzylpiperidin-4-yl, 1-(pyridin-3-yl)piperidin-4-yl, 1-(pyridin-2-yl)piperidin-4-yl, 1-acetyl piperidin-4-yl, 1,1-dioxidotetrahydrothiopyran-4-yl, 2-azaspiro[3.3]heptan-6-yl, 2-azaspiro[3.5]nonan-7-yl, 8-phenyl-8-azabicyclo[3.2.1]octan-3-yl, or 3-azaspiro[5.5]undecan-9-yl.

52. The compound of any one of claims 1 to 5, 16, and 46 to 51, wherein R^1 is 1-phenylpiperidin-3-yl, 1-phenylpiperidin-4-yl, 1-(3-chlorophenyl)piperidin-4-yl, or 1-(4-chlorophenyl)piperidin-4-yl.

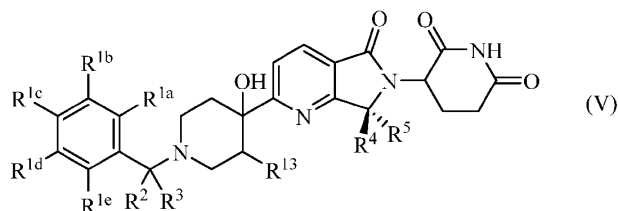
53. The compound of claim 1, 4, or 5, having the structure of Formula (IV):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof; wherein:

R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each independently H, deuterium, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S(O)}_2\text{R}'$, or $-\text{S(O)}_2\text{NR}'\text{R}''$; or R^{1a} and R^{1b} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl; or R^{1b} and R^{1c} together with the carbon atoms to which they are attached form substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

54. The compound of claim 53, having the structure of Formula (V):



or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; or a pharmaceutically acceptable derivative thereof.

55. The compound of claim 53 or 54, wherein R^{1a} , R^{1b} , R^{1c} , R^{1d} , and R^{1e} are each independently H, deuterium, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S(O)}_2\text{R}'$, or $-\text{S(O)}_2\text{NR}'\text{R}''$.

56. The compound of any one of claims 53 to 55, wherein R^{1a} is H, deuterium, cyano, halo, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_1 - C_{10} heteroalkyl, substituted or unsubstituted C_3 - C_{10} cycloalkyl, substituted or unsubstituted C_6 - C_{14} aryl, substituted or unsubstituted C_7 - C_{15} arylalkyl, substituted or unsubstituted heteroaryl, substituted

or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$.

57. The compound of any one of claims 53 to 56, wherein R^{1a} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidinyl, difluoropiperidinyl, (hydroxymethyl)piperidinyl, hydroxypiperidinyl, oxanyl, morpholino, 8-azabicyclo[3.2.1]-octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl.

58. The compound of any one of claims 53 to 57, wherein R^{1a} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yl-oxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl.

59. The compound of any one of claims 53 to 58, wherein R^{1a} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo-[3.2.1]octan-8-yl, or phenoxy.

60. The compound of any one of claims 53 to 59, wherein R^{1a} is H.

61. The compound of any one of claims 53 to 60, wherein R^{1b} is H, deuterium, cyano, halo, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ heteroalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl, substituted or unsubstituted $\text{C}_7\text{-C}_{15}$ arylalkyl, substituted or unsubstituted heteroaryl, substituted

or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$.

62. The compound of any one of claims 53 to 61, wherein R^{1b} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidinyl, difluoropiperidinyl, (hydroxymethyl)piperidinyl, hydroxypiperidinyl, oxanyl, morpholino, 8-azabicyclo[3.2.1]-octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl.

63. The compound of any one of claims 53 to 62, wherein R^{1b} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yl-oxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl.

64. The compound of any one of claims 53 to 63, wherein R^{1b} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo-[3.2.1]octan-8-yl, or phenoxy.

65. The compound of any one of claims 53 to 64, wherein R^{1c} is H, deuterium, cyano, halo, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted or unsubstituted $\text{C}_1\text{-C}_{10}$ heteroalkyl, substituted or unsubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted or unsubstituted $\text{C}_6\text{-C}_{14}$ aryl, substituted or unsubstituted $\text{C}_7\text{-C}_{15}$ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, $-\text{COR}'$, $-\text{CONR}'\text{R}''$, $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{S}(\text{O})_2\text{R}'$, or $-\text{S}(\text{O})_2\text{NR}'\text{R}''$.

66. The compound of any one of claims 53 to 65, wherein R^{1c} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, difluoroethyl, propyl, butyl, oxanylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazolyl, methylpyrazolyl, oxetanyl, piperidinyl, difluoropiperidinyl, (hydroxymethyl)piperidinyl, hydroxypiperidinyl, oxanyl, morpholino, 8-azabicyclo[3.2.1]-octanyl, hydroxyl, methoxy, trifluoromethoxy, hydroxyethoxy, phenoxy, benzoxy, oxanyloxy, piperidinyloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl.

67. The compound of any one of claims 53 to 66, wherein R^{1c} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, morpholinomethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclobutyl, cyclohexyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, 2-methylpyrazol-3-yl, oxetan-3-yl, oxan-4-yl, piperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-(hydroxymethyl)piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 8-azabicyclo[3.2.1]octan-8-yl, hydroxyl, methoxy, trifluoromethoxy, 2-hydroxyethoxy, phenoxy, benzoxy, piperidin-4-yl-oxy, oxan-4-yloxy, amino, dimethylamino, phenylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulfonyl, or aminosulfonyl.

68. The compound of any one of claims 53 to 67, wherein R^{1c} is H, cyano, chloro, fluoro, methyl, trifluoromethyl, ethyl, 1,1-difluoroethyl, isopropyl, *tert*-butyl, oxan-4-ylmethyl, methoxymethyl, phenyl, pyrazol-1-yl, 1-methylpyrazol-3-yl, 1-methylpyrazol-4-yl, piperidin-1-yl, morpholino, 8-azabicyclo-[3.2.1]octan-8-yl, or phenoxy.

69. The compound of any one of claims 53 to 68, wherein R^{1d} is H.

70. The compound of any one of claims 53 to 69, wherein R^{1e} is H.

71. The compound of any one of claims 53 to 55 and 65 to 68, wherein R^{1a} and R^{1b} together with the carbon atoms to which they are attached form heteroaryl or heterocycloalkyl, each optionally substituted with one, two, or three substituents, each of which is independently deuterium, oxo, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or

unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

72. The compound of any one of claims 53 to 55 and 65 to 69, wherein R^{1a} and R^{1b} together with the carbon atoms to which they are attached form tetrahydrofuran-2,3-diyl, 5,5-dimethyl-tetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyrrolidin-3,4-diyl, 2-oxopyrrolidin-3,4-diyl, 2,2-difluoro-1,3-dioxolan-4,5-diyl, 2,2-dimethyl-1,3-dioxolan-4,5-diyl, oxan-2,3-diyl, 4-methyl-morpholin-2,3-diyl, or 5-oxomorpholin-2,3-diyl.

73. The compound of any one of claims 53 to 60, 69, and 70, wherein R^{1b} and R^{1c} together with the carbon atoms to which they are attached form heteroaryl or heterocycloalkyl, each optionally substituted with one, two, or three substituents, each of which is independently deuterium, oxo, cyano, halo, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₁-C₁₀ heteroalkyl, substituted or unsubstituted C₃-C₁₀ cycloalkyl, substituted or unsubstituted C₆-C₁₄ aryl, substituted or unsubstituted C₇-C₁₅ arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycloalkyl, -COR', -CONR'R", -OR', -NR'R", -S(O)₂R', or -S(O)₂NR'R".

74. The compound of any one of claims 53 to 60 and 69 to 73, wherein R^{1b} and R^{1c} together with the carbon atoms to which they are attached form tetrahydrofuran-2,3-diyl, 5,5-dimethyl-tetrahydrofuran-2,3-diyl, tetrahydrofuran-3,4-diyl, pyrrolidin-3,4-diyl, 2-oxopyrrolidin-3,4-diyl, 2,2-difluoro-1,3-dioxolan-4,5-diyl, 2,2-dimethyl-1,3-dioxolan-4,5-diyl, oxan-2,3-diyl, 4-methyl-morpholin-2,3-diyl, or 5-oxomorpholin-2,3-diyl.

75. The compound of any one of claims 1 to 74, wherein R² is H.

76. The compound of any one of claims 1 to 75, wherein R³ is H.

77. The compound of any one of claims 1 to 74, wherein R² and R³ together with the carbon atom to which they are attached form C(O).

78. The compound of any one of claims 1 to 77, wherein R⁴ is H, or substituted or unsubstituted C₁-C₁₀ alkyl.

79. The compound of any one of claims 1 to 78, wherein R⁴ is H.
80. The compound of any one of claims 1 to 78, wherein R⁴ is methyl.
81. The compound of any one of claims 1 to 80, wherein R⁵ is H, or substituted or unsubstituted C₁-C₁₀ alkyl.
82. The compound of any one of claims 1 to 81, wherein R⁵ is H.
83. The compound of any one of claims 1 to 82, wherein R⁵ is methyl.
84. The compound of any one of claims 1 to 83, wherein R¹³ is H.
85. The compound of any one of claims 1 to 83, wherein R¹³ is hydroxyl.
86. The compound of claim 1, wherein the compound is:
- 3-(2-(1-benzyl-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A001**;
- 3-(2-(4-hydroxy-1-(pyridin-4-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A002**;
- 3-(2-(4-hydroxy-1-(2-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A003**;
- 3-(2-(4-hydroxy-1-(4-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A004**;
- 3-(2-(4-hydroxy-1-phenethylpiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A005**;
- 3-(2-(4-hydroxy-1-(2-hydroxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A006**;
- 3-(2-(4-hydroxy-1-(3-hydroxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A007**;
- 3-(2-(4-hydroxy-1-(2-cyanobenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A008**;
- 3-(2-(4-hydroxy-1-(4-cyanobenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A009**;

3-(2-(4-hydroxy-1-(3-cyanobenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A010**;

3-(2-(4-hydroxy-1-(4-(hydroxymethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A011**;

3-(2-(1-(4-chlorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A012**;

3-(2-(1-(2,4-difluorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A013**;

3-(2-(1-(4-(dimethylamino)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A014**;

3-(2-(1-([1,1'-biphenyl]-4-ylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A015**;

3-(2-(4-hydroxy-1-(4-(methylsulfonyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A016**;

3-(2-(4-hydroxy-1-(3-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A017**;

3-(2-(4-hydroxy-1-(3-phenoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A018**;

3-(2-(1-(cyclohexylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A019**;

3-(2-(4-hydroxy-1-(3-methylbenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A020**;

3-(2-(1-(3-aminobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A021**;

3-(2-(4-hydroxy-1-((2-oxo-1,2-dihydropyridin-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A022**;

3-(2-(4-hydroxy-1-(2-methoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A023**;

3-(2-(4-hydroxy-1-(3-methoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A024**;

3-(2-(4-hydroxy-1-(4-methoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A025**;

3-(2-(1-(3-chlorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A026**;

3-(2-(1-(benzofuran-6-ylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A027**;

3-(2-(1-((1*H*-indazol-5-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A028**;

3-(2-(4-hydroxy-1-(pyrazolo[1,5-*a*]pyridin-6-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A029**;

3-(2-(1-((2,3-dihydro-1*H*-inden-2-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A030**;

3-(2-(4-hydroxy-1-(4-aminocarbonylphenylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A031**;

3-(2-(4-hydroxy-1-(3-aminocarbonylphenylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A032**;

3-(2-(1-(3-(dimethylamino)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A033**;

3-(2-(4-hydroxy-1-(4-(methoxymethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A034**;

3-(2-(4-hydroxy-1-(quinolin-6-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A035**;

3-(2-(4-hydroxy-1-((1-methyl-1*H*-indazol-6-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A036**;

3-(2-(1-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A037**;

3-(2-(4-hydroxy-1-((1-phenyl-1*H*-pyrazol-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A038**;

3-(2-(4-hydroxy-1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A039**;

4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)-*N,N*-dimethylbenzamide **A040**;

3-(2-(1-((2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A041**;

3-(2-(4-hydroxy-1-(4-(trifluoromethoxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A042**;

3-(2-(1-(4-(benzyloxy)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A043**;

3-(2-(4-hydroxy-1-((1-methyl-1*H*-indazol-5-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A044**;

3-(2-(4-hydroxy-1-((1-methyl-1*H*-pyrazol-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A045**;

4-((4-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)-*N*-methylbenzamide **A046**;

3-(2-(4-hydroxy-1-((1-(trifluoromethyl)-1*H*-pyrazol-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A047**;

3-(2-(4-hydroxy-1-(4-(1-methyl-1*H*-pyrazol-4-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A048**;

3-(2-(4-hydroxy-1-((1-phenylpiperidin-4-yl)methyl)piperidin-4-yl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A049**;

3-(2-(4-hydroxy-1-(4-(phenylamino)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A050**;

3-(2-(4-hydroxy-1-(4-(4-hydroxypiperidin-1-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A051**;

3-(2-(1-((1*H*-pyrrolo[3,2-*b*]pyridin-6-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A052**;

3-(2-(1-((2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A053**;

3-(2-(1-((2,2-dimethyl-2,3-dihydrobenzofuran-6-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A054**;

3-(2-(4-hydroxy-1-(isoxazol-4-ylmethyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A055**;

3-(2-(4-hydroxy-1-((tetrahydro-2H-pyran-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A056**;

3-(2-(4-hydroxy-1-((1-methyl-1H-benzo[*d*][1,2,3]triazol-5-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A057**;

3-(2-(1-(4-((dimethylamino)methyl)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A058**;

3-(2-(4-hydroxy-1-(4-phenoxybenzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A059**;

3-(2-(4-hydroxy-1-(4-((tetrahydro-2H-pyran-4-yl)oxy)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A060**;

3-(2-(4-hydroxy-1-(4-(4-(hydroxymethyl)piperidin-1-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A061**;

3-(2-(4-hydroxy-1-(4-(phoxymethyl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A062**;

3-(2-(1-((1-(3-chlorophenyl)-4-piperidyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A063**;

3-(2-(1-((1-(2-chlorophenyl)-4-piperidyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A064**;

3-(2-(1-((1-(4-chlorophenyl)piperidin-4-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A065**;

3-(2-(4-hydroxy-1-((4-(1-methylpyrazol-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A066**;

3-(2-(4-hydroxy-1-((4-(2-methylpyrazol-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A067**;

3-(2-(4-hydroxy-1-((4-pyrazol-1-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A068**;

3-(2-(4-hydroxy-1-((1-(2-pyridyl)-4-piperidyl)methyl)-4-piperidyl)-5-oxo-7H-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A069**;

3-(2-(4-hydroxy-1-(((*R*)-1-phenylpiperidin-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A070**;

3-(2-(4-hydroxy-1-((1-(pyridin-3-yl)piperidin-4-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A071**;

3-(2-(4-hydroxy-1-((8-phenyl-8-azabicyclo[3.2.1]octan-3-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A072**;

3-(2-(4-hydroxy-1-((1-phenylazetidin-3-yl)methyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A073**;

3-(2-(1-(4-chlorobenzoyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A074**;

3-(2-(1-(3,4-dimethoxybenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A075**;

3-(2-(4-hydroxy-1-((1-methylindol-5-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A076**;

3-(2-(4-hydroxy-1-((1-methylindazol-4-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A077**;

3-(2-(4-hydroxy-1-((4-(oxetan-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A078**;

3-(2-(4-hydroxy-1-((3-(1-piperidyl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A079**;

3-(2-(1-((4-(4,4-difluoro-1-piperidyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A080**;

3-(2-(4-hydroxy-1-(4-(piperidin-1-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A081**;

3-(2-(4-hydroxy-1-((4-tetrahydropyran-4-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A082**;

3-(2-(4-hydroxy-1-(3-(tetrahydro-2*H*-pyran-4-yl)benzyl)piperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A083**;

3-(2-(1-((3-fluorophenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A084**;

3-(2-(4-hydroxy-1-((4-morpholinophenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A085**;

3-(2-(4-hydroxy-1-((3-morpholinophenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A086**;

3-(2-(4-hydroxy-1-((3-(oxetan-3-yl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo-[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A087**;

3-(2-(4-hydroxy-1-((4-(tetrahydropyran-4-yl)methyl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A088**;

3-(2-(1-((2-fluorophenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A089**;

3-(2-(4-hydroxy-1-isobutyl-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-piperidine-2,6-dione **A090**;

3-(2-(1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A091**;

3-(2-(4-hydroxy-1-((1-methylbenzimidazol-5-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A092**;

3-(2-(4-hydroxy-1-((3-methylbenzimidazol-5-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A093**;

3-(2-(4-hydroxy-1-((1-methylindol-6-yl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A094**;

3-(2-(4-hydroxy-1-((4-(morpholinomethyl)phenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A095**;

3-(2-(1-((4-fluorophenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A096**;

(3*S*)-3-((7*S*)-2-(1-benzyl-4-hydroxy-4-piperidyl)-7-methyl-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A097**;

(*S*)-3-((*R*)-2-(4-hydroxy-1-((1-phenylpiperidin-4-yl)methyl)piperidin-4-yl)-7-methyl-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A098**;

3-(2-(1-(2-(3-fluorophenyl)ethyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A099**;

3-(2-(1-(chroman-7-ylmethyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]-pyridin-6-yl)piperidine-2,6-dione **A100**;

3-(2-(1-(chroman-6-ylmethyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A101**;

3-(2-(1-((2,3-dihydrobenzofuran-6-yl)methyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A102**;

3-(2-(1-(2,3-dihydrobenzofuran-5-ylmethyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A103**;

3-(2-(1-(1,3-dihydroisobenzofuran-5-ylmethyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A104**;

3-(2-((3*S*,4*S*)-1-benzyl-3,4-dihydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A105**;

3-(2-((3*R*,4*R*)-1-benzyl-3,4-dihydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A106**;

3-(2-(1-((3,4-bis(trifluoromethyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A107**;

3-(2-(1-((4-*tert*-butylphenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A108**;

3-(2-(1-((3-*tert*-butylphenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A109**;

3-(2-(4-hydroxy-1-((4-isopropylphenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]-pyridin-6-yl)piperidine-2,6-dione **A110**;

3-(2-(4-hydroxy-1-((3-isopropylphenyl)methyl)-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]-pyridin-6-yl)piperidine-2,6-dione **A111**;

3-(2-(1-((3-(1,1-difluoroethyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A112**;

3-(2-(1-((4-(1,1-difluoroethyl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A113**;

3-(2-(1-(4-ethylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A114**;

3-(2-(1-(4-chloro-3-methylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A115**;

3-(2-(1-(4-(((1*R*,5*S*)-8-azabicyclo[3.2.1]octan-8-yl)benzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A116**;

3-(2-(1-(4-cyclobutylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A117**;

3-(2-(1-(3-ethylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A118**;

3-(2-(1-(4-chloro-3-fluorobenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A119**;

3-(2-(1-(3-cyclobutylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A120**;

3-(2-(1-(((1*R*,5*S*)-8-azabicyclo[3.2.1]octan-8-yl)phenyl)methyl)-4-hydroxy-4-piperidyl)-5-oxo-7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A121**;

3-(2-(1-(4-cyclohexylbenzyl)-4-hydroxypiperidin-4-yl)-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A122**;

4-((4-(6-((*S*)-2,6-dioxopiperidin-3-yl)-7-methyl-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile **A123**;

4-((4-((*R*)-6-((*S*)-2,6-dioxopiperidin-3-yl)-7-methyl-5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-2-yl)-4-hydroxypiperidin-1-yl)methyl)benzonitrile **A124**;

3-(2-{4-hydroxy-1-[(1*H*-pyrazol-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A125**;

3-(2-{4-hydroxy-1-[(1,3-oxazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A126**;

3-(2-{4-hydroxy-1-[(1*H*-1,2,4-triazol-3-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A127**;

3-(2-{4-hydroxy-1-[(pyridin-3-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A128**;

3-(2-{4-hydroxy-1-[(pyridin-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A129**;

- 3-(2-{4-hydroxy-1-[(1-methyl-1*H*-pyrazol-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A130**;
- 3-(2-{4-hydroxy-1-[(1,3-thiazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A131**;
- 3-(2-{4-hydroxy-1-[(piperidin-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A132**;
- 3-(2-{4-hydroxy-1-[(oxan-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A133**;
- 3-(2-{4-hydroxy-1-[(oxan-3-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A134**;
- 3-(2-{4-hydroxy-1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A135**;
- 3-{2-[1-({2-azaspiro[3.3]heptan-6-yl)methyl}-4-hydroxypiperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A136**;
- 3-(2-{4-hydroxy-1-[(5-methyl-1,3-thiazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A137**;
- 3-[2-(4-hydroxy-1-{[(1*r*,4*r*)-4-aminocyclohexyl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A138**;
- 3-{2-[4-hydroxy-1-({5*H*,6*H*,7*H*-pyrrolo[1,2-*a*]imidazol-2-yl)methyl]piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A139**;
- 3-(2-{4-hydroxy-1-[(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A140**;
- 3-[2-(4-hydroxy-1-{[1-(propan-2-yl)-1*H*-pyrazol-4-yl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A141**;
- 3-{2-[4-hydroxy-1-({imidazo[1,2-*a*]pyridin-2-yl)methyl]piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A142**;
- 3-{2-[4-hydroxy-1-({1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)methyl]piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A143**;
- 3-(2-{1-[(1,3-benzoxazol-2-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A144**;

3-{2-[4-hydroxy-1-({[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)methyl}piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A145**;

3-(2-{1-[(2,3-dihydro-1*H*-isoindol-5-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A146**;

3-{2-[4-hydroxy-1-({4*H*,5*H*,6*H*,7*H*-pyrazolo[1,5-*a*]pyridin-3-yl)methyl}-piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A147**;

3-{2-[1-({4*H*,5*H*,6*H*-cyclopenta[*d*][1,3]thiazol-2-yl)methyl]-4-hydroxypiperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A148**;

3-{2-[1-({2-azaspiro[3.5]nonan-7-yl)methyl]-4-hydroxypiperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A149**;

3-(2-{1-[(1-acetyl)piperidin-4-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A150**;

3-[2-(4-hydroxy-1-{[1-(propan-2-yl)piperidin-4-yl)methyl}piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A151**;

3-(2-{4-hydroxy-1-[(quinolin-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A152**;

3-(2-{4-hydroxy-1-[(3-oxo-2,3-dihydro-1*H*-isoindol-5-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A153**;

3-[(4-{6-[2,6-dioxopiperidin-3-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-2-yl}-4-hydroxypiperidin-1-yl)methyl]-*N*-methylbenzamide **A154**;

3-(2-{1-[(1,3-benzothiazol-2-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A155**;

3-[2-(4-hydroxy-1-{[4-(2-hydroxyethoxy)phenyl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A156**;

3-[2-(4-hydroxy-1-{[4-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A157**;

3-(2-{4-hydroxy-1-[(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)methyl]-piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A158**;

3-{2-[4-hydroxy-1-({4-methyl-2*H*,3*H*,4*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)methyl}-piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A159**;

3-{2-[1-({3-azaspiro[5.5]undecan-9-yl}methyl)-4-hydroxypiperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A160**;

4-[(4-{6-[2,6-dioxopiperidin-3-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-2-yl}-4-hydroxypiperidin-1-yl)methyl]benzene-1-sulfonamide **A161**;

3-(2-{4-hydroxy-1-[(5-methyl-1*H*-pyrazol-4-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A162**;

3-(2-{4-hydroxy-1-[(5-methyl-1,3,4-thiadiazol-2-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A163**;

3-[2-(4-hydroxy-1-{[1-(propan-2-yl)-1*H*-pyrazol-3-yl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A164**;

3-{2-[4-hydroxy-1-({1*H*-pyrrolo[3,2-*b*]pyridin-2-yl}methyl)piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A165**;

3-{2-[4-hydroxy-1-({5*H*,6*H*,7*H*,8*H*-imidazo[1,2-*a*]pyridin-2-yl}methyl)piperidin-4-yl]-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl}piperidine-2,6-dione **A166**;

3-[2-(4-hydroxy-1-{[4-(piperidin-4-yloxy)phenyl]methyl}piperidin-4-yl)-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl]piperidine-2,6-dione **A167**;

3-(2-{1-[(1-benzylpiperidin-4-yl)methyl]-4-hydroxypiperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A168**; or

3-(2-{4-hydroxy-1-[(quinolin-3-yl)methyl]piperidin-4-yl}-5-oxo-5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-6-yl)piperidine-2,6-dione **A169**;

or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

87. A pharmaceutical composition comprising the compound of any one of claims 1 to 86, or an enantiomer, a mixture of enantiomers, a diastereomer, a mixture of two or more diastereomers, a tautomer, or a mixture of two or more tautomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a pharmaceutically acceptable excipient.

88. The pharmaceutical composition of claim 87, wherein the pharmaceutical composition is in single dosage form.

89. The pharmaceutical composition of claim 87 or 88, wherein the pharmaceutical composition is in an oral, parenteral, or intravenous dosage form.

90. The pharmaceutical composition of any one of claims 87 to 89, wherein the pharmaceutical composition is formulated in an oral dosage form.

91. The pharmaceutical composition of claim 90, wherein the oral dosage form is a tablet or capsule.

92. A method of treating, preventing, or ameliorating one or more symptoms of a disorder or disease mediated by an ARNT in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 86 or a pharmaceutical composition of any one of claims 87 to 91.

93. The method of claim 92, wherein the disease or disorder is cancer, inflammation, or an autoimmune disorder.

94. A method of treating, preventing, or ameliorating one or more symptoms of a proliferative disease in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 86 or a pharmaceutical composition of any one of claims 87 to 91.

95. The method of claim 94, wherein the proliferative disease is cancer.

96. The method of any one of claims 92 to 95, wherein the subject is a human.

97. A method of inhibiting the growth of a cell, comprising contacting the cell with an effective amount of a compound of any one of claims 1 to 86 or a pharmaceutical composition of any one of claims 87 to 91.

98. The method of claim 97, wherein the cell is a cancerous cell.

99. A method of inducing degradation of an ARNT, comprising contacting the ARNT with an effective amount of a compound of any one of claims 1 to 86 or a pharmaceutical composition of any one of claims 87 to 91.

100. A method of inhibiting the activity of an ARNT, comprising contacting the ARNT with an effective amount of a compound of any one of claims 1 to 86 or a pharmaceutical composition of any one of claims 87 to 91.