

**PIPERIDINYL-METHYL-PURINEAMINE NSD2 INHIBITOR THERAPEUTIC
METHODS AND COMPOSITIONS FOR TREATING CANCER**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/727,941, filed on December 4, 2024, and U.S. Provisional Application No. 63/616,928, filed on January 2, 2024; the contents of each of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention provides methods and compositions for using a piperidinyl-methyl-purineamine nuclear SET domain-containing protein 2 (NSD2) inhibitor to treat cancer, such as combination therapies to treat cancer.

BACKGROUND

[0003] Cancer continues to be a significant health problem despite the substantial research efforts and scientific advances reported in the literature for treating this disease. Solid tumors, including breast cancer, lung cancer, colorectal cancer, and pancreatic cancer remain prevalent among the world population. Current treatment options for these cancers are not effective for all patients and/or can have substantial adverse side effects. New therapies are needed to address this unmet need in cancer therapy.

[0004] The nuclear receptor-binding SET domain protein 2 (NSD2), also known as Wolf-Hirschhorn syndrome candidate 1 (WHSC1) or multiple myeloma SET domain (MMSET) is an epigenetic modifier, and is believed to have a driving role in oncogenesis. Both NSD2 overexpression and point mutations that increase its catalytic activity are associated with several human cancers. (Coussens et al., J. Biol. Chem. 293, 13750-13654 (2018).

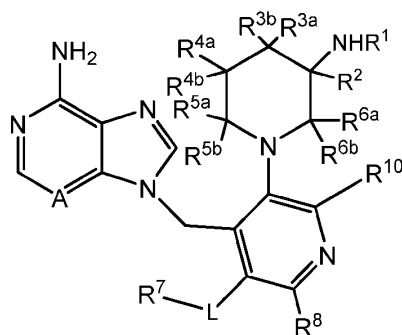
[0005] NSD2 is dysregulated by the t(4;14)(p16.3;q32.3) translocation in approximately 15% of multiple myeloma (MM) cases. Increased expression of NSD2 in t(4;14)+ MM cell lines is associated with increased levels of H3K36me2 and reciprocally decreased levels of H3K27me3. Such correlation suggests a causal relationship between NSD2 histone methyltransferase (HMT) activity and the MM oncogene.

[0006] High expression of the NSD2 protein has been demonstrated in different human cancer types, including bladder, brain, gastrointestinal, lung, liver, ovary, skin, uterus, breast, prostate and glioblastoma. (Coussens et al., supra; Ezponda et al., *Oncogene* 32:2882-2890 (2013)). Notably, NSD2 is among the most frequently mutated genes in pediatric cancer genomes. The NSD2 SET domain variant, E1099K, was identified in both acute lymphoblastic leukemia tumors and cell lines with increased H3K36me2 that lack the t(4;14) translocation. Sequence results of >1000 pediatric cancer genomes, representing 21 different cancers, revealed the E1099K variant in 14% of t(12;21) ETV6 -RUNX1 containing acute lymphoblastic leukemia (ALL). NSD2 is also among the most frequently mutated genes found in mantle cell lymphoma tumors, where both E1099K and T1150A variants are observed. The E1099K variant has also been reported in chronic lymphocytic leukemia (CLL), lung and stomach cancers. (Coussens et al., supra). In general, NSD2 upregulation is associated with aggressive tumor behavior and poor prognosis. (Ezponda et al., supra).

[0007] New therapies are needed to treat cancer. The present invention addresses the foregoing needs and provides other related advantages.

SUMMARY

[0008] The present invention provides methods and compositions for using a piperidiny-methyl-purineamine nuclear SET domain-containing protein 2 (NSD2) inhibitor to treat cancer, such as combination therapies to treat cancer. One aspect of the invention provides a method of treating cancer, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount of a first therapeutic agent and a second therapeutic agent to treat the cancer, wherein the first therapeutic agent is a compound of Formula I:

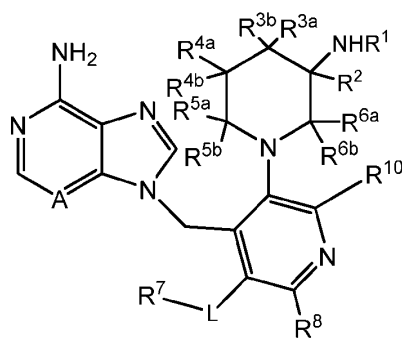


(I)

or a pharmaceutically acceptable salt thereof, wherein variable definitions are as described herein below; and the second therapeutic agent is (i) daratumumab, isatuximab, idecabtegene vicleucel, ciltacabtegene autoleucel, or belantamab mafodotin-blmf, (ii) bortezomib, carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, mezigdomide, iberdomide, selinexor, binemetinib, cobimetinib, selumetinib, refametinib, PD-0325901, or ROS126766, or a pharmaceutically acceptable salt thereof, (iii) dacomitinib, mobercitinib, neratinib, osimertinib, or vandetenib, or a pharmaceutically acceptable salt thereof, (iv) a bispecific antibody that binds CD3, (v) a tagged antibody, (vi) a chimeric antigen receptor (CAR) T-cell therapy cell therapy or a natural killer (NK) cell therapy, (vii) a natural killer cell engager, (viii) a KRAS inhibitor, (ix) an immune checkpoint inhibitor, (x) an FGFR3 inhibitor, (xi) an androgen receptor inhibitor, (xii) a BCL-2, BCLXL, or MCL1 inhibitor, (xiii) PARP inhibitor, (xiv) an androgen receptor degrader, or (xv) a radioligand therapy agent.

[0009] Pharmaceutical compositions containing a first therapeutic agent described herein, a second therapeutic agent described herein, and a pharmaceutically acceptable carrier are provided.

[0010] Another aspect of the invention provides a method of treating cancer, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I to treat the cancer, wherein Formula I is represented by:



(I)

or a pharmaceutically acceptable salt thereof, wherein variable definitions are as described herein below. In certain embodiments, the cancer is a metastatic prostate cancer, such as metastatic

castration-resistant prostate cancer (mCRPC) or metastatic castration-sensitive prostate cancer (mCSPC).

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] **FIGURE 1** depicts graphs showing results of a cell adhesion assay, as further described in Example 1.

[0012] **FIGURE 2** depicts a graph showing results of anti-cancer assays, as further described in Example 2.

[0013] **FIGURE 3** depicts a graph showing results of anti-cancer assays, as further described in Example 2.

[0014] **FIGURE 4** depicts a graph showing results of anti-cancer assays, as further described in Example 3.

[0015] **FIGURE 5** depicts a graph showing results of anti-cancer assays, as further described in Example 3.

[0016] **FIGURE 6** depicts graphs showing results of anti-cancer assays, as further described in Example 4.

[0017] **FIGURE 7** depicts a graph showing results of anti-cancer assays, as further described in Example 5.

[0018] **FIGURE 8** depicts a graph showing results of anti-cancer assays, as further described in Example 5.

[0019] **FIGURE 9** depicts a graph showing results of anti-cancer assays, as further described in Example 6.

[0020] **FIGURE 10** depicts a graph showing results of anti-cancer assays, as further described in Example 6

[0021] **FIGURE 11** depicts a graph showing results of anti-cancer assays, as further described in Example 7.

[0022] **FIGURE 12** depicts a graph showing results of anti-cancer assays, as further described in Example 8.

DETAILED DESCRIPTION

[0023] The present invention provides methods and compositions for using a piperidinyl-methyl-purineamine nuclear SET domain-containing protein 2 (NSD2) inhibitor to treat cancer, such as combination therapies to treat cancer. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology. Such techniques are explained in the literature, such as in “Comprehensive Organic Synthesis” (B.M. Trost & I. Fleming, eds., 1991-1992); “Handbook of experimental immunology” (D.M. Weir & C.C. Blackwell, eds.); “Current protocols in molecular biology” (F.M. Ausubel *et al.*, eds., 1987, and periodic updates); and “Current protocols in immunology” (J.E. Coligan *et al.*, eds., 1991), each of which is herein incorporated by reference in its entirety.

[0024] Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section. Further, when a variable is not accompanied by a definition, the previous definition of the variable controls.

Definitions

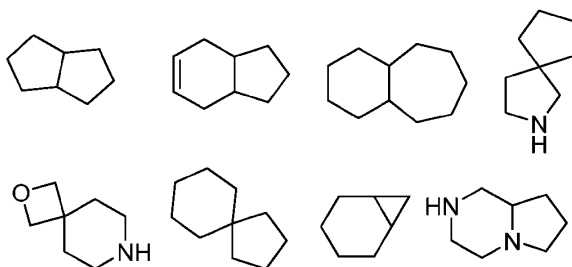
[0025] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of “alkyl” applies to “alkyl” as well as the “alkyl” portions of “-O-alkyl” etc. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in “Organic Chemistry”, Thomas Sorrell, University Science Books, Sausalito: 1999, and “March’s Advanced Organic Chemistry”, 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0026] The term “aliphatic” or “aliphatic group”, as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or

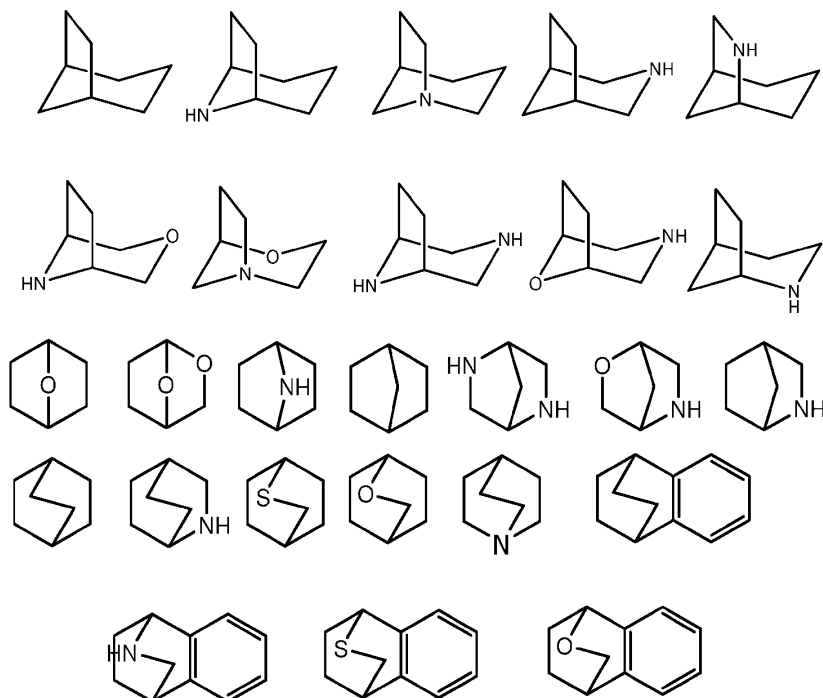
bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as “cycloaliphatic”), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, “cycloaliphatic” refers to a monocyclic C₃-C₆ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0027] As used herein, the term “bicyclic ring” or “bicyclic ring system” refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or having one or more units of unsaturation, having one or more atoms in common between the two rings of the ring system. Thus, the term includes any permissible ring fusion, such as *ortho*-fused or spirocyclic. As used herein, the term “heterobicyclic” is a subset of “bicyclic” that requires that one or more heteroatoms are present in one or both rings of the bicycle. Such heteroatoms may be present at ring junctions and are optionally substituted, and may be selected from nitrogen (including N-oxides), oxygen, sulfur (including oxidized forms such as sulfones and sulfonates), phosphorus (including oxidized forms such as phosphates), boron, etc. In some embodiments, a bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. As used herein, the term “bridged bicyclic” refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a “bridge” is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a “bridgehead” is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more

substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bicyclic rings include:



[0028] Exemplary bridged bicyclics include:



[0029] The term “lower alkyl” refers to a C₁₋₄ straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0030] The term “lower haloalkyl” refers to a C₁₋₄ straight or branched alkyl group that is substituted with one or more halogen atoms.

[0031] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized

form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

[0032] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation.

[0033] As used herein, the term “bivalent C₁₋₈ (or C₁₋₆) saturated or unsaturated, straight or branched, hydrocarbon chain”, refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

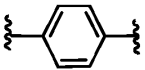
[0034] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., -(CH₂)_n-, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

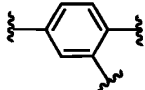
[0035] The term “-(C₀ alkylene)-” refers to a bond. Accordingly, the term “-(C₀₋₃ alkylene)-” encompasses a bond (i.e., C₀) and a -(C₁₋₃ alkylene)- group.

[0036] The term “alkenylene” refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0037] The term “halogen” means F, Cl, Br, or I.

[0038] The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” “aralkoxy,” or “aryloxyalkyl,” refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term “aryl” may be used interchangeably with the term “aryl ring.” In certain embodiments of the present invention, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term “aryl,” as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like. The term “phenylene” refers to a multivalent phenyl group having the appropriate number of open valences to account for groups attached to it. For example, “phenylene” is a bivalent phenyl group

when it has two groups attached to it (e.g., ); “phenylene” is a trivalent phenyl group

when it has three groups attached to it (e.g., ). The term “arylene” refers to a bivalent aryl group.

[0039] The terms “heteroaryl” and “heteroar–,” used alone or as part of a larger moiety, e.g., “heteroaralkyl,” or “heteroaralkoxy,” refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term “heteroatom” refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizynyl, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar–,” as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where unless otherwise specified, the radical or point of attachment is on the heteroaromatic ring or on one of the rings to which the heteroaromatic ring is fused. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolynyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinolizynyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolynyl, and tetrahydroisoquinolynyl. A heteroaryl group may be mono- or bicyclic. The term “heteroaryl” may be used interchangeably with the terms “heteroaryl ring,” “heteroaryl group,” or “heteroaromatic,” any of which terms include rings that are optionally substituted. The term “heteroaralkyl” refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0040] As used herein, the terms “heterocycle,” “heterocyclyl,” “heterocyclic radical,” and “heterocyclic ring” are used interchangeably and refer to a stable 5- to 7-membered monocyclic or 7-10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term “nitrogen” includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0-3

heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0041] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, 2-oxa-6-azaspiro[3.3]heptane, and quinuclidinyl. The terms “heterocycle,” “heterocyclyl,” “heterocyclyl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be mono- or bicyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted. The term “oxo-heterocyclyl” refers to a heterocyclyl substituted by an oxo group. The term “heterocyclylene” refers to a multivalent heterocyclyl group having the appropriate number of open valences to account for groups attached to it. For example, “heterocyclylene” is a bivalent heterocyclyl group when it has two groups attached to it; “heterocyclylene” is a trivalent heterocyclyl group when it has three groups attached to it.

[0042] As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0043] As described herein, compounds of the invention may contain “optionally substituted” moieties. In general, the term “substituted,” whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by

this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0044] Each optional substituent on a substitutable carbon is a monovalent substituent independently selected from halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}pyridyl$ which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-S(O)(NR^\circ)R^\circ$; $-S(O)_2N=C(NR^\circ_2)_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ$; $-OP(O)R^\circ$; $-OP(O)(OR^\circ)_2$; SiR°_3 ; $-(C_{1-4}$ straight or branched alkylene) $O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^\circ)_2$.

[0045] Each R° is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2-(5-6$ membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted by a divalent substituent on a saturated carbon atom of R° selected from $=O$ and $=S$; or each R° is optionally substituted with a monovalent substituent independently selected from halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$, $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}C(O)SR^\bullet$, $-(CH_2)_{0-2}C(O)OSiR^\bullet_3$, $-(CH_2)_{0-2}OC(O)R^\bullet$, $-OC(O)(CH_2)_{0-2}SR^\bullet$, $SC(S)SR^\bullet$, $-(CH_2)_{0-2}SC(O)R^\bullet$, $-(CH_2)_{0-2}C(O)NR^\bullet_2$, $-C(S)NR^\bullet_2$, $-C(S)SR^\bullet$, $-SC(S)SR^\bullet$, $-(CH_2)_{0-2}OC(O)NR^\bullet_2$, $-C(O)N(OR^\bullet)R^\bullet$, $-C(O)C(O)R^\bullet$, $-C(O)CH_2C(O)R^\bullet$, $-C(NOR^\bullet)R^\bullet$, $-(CH_2)_{0-2}SSR^\bullet$, $-(CH_2)_{0-2}S(O)_2R^\bullet$, $-(CH_2)_{0-2}S(O)_2OR^\bullet$, $-(CH_2)_{0-2}OS(O)_2R^\bullet$, $-S(O)_2NR^\bullet_2$, $-S(O)(NR^\bullet)R^\bullet$, $-S(O)_2N=C(NR^\bullet_2)_2$, $-(CH_2)_{0-2}S(O)R^\bullet$, $-N(R^\bullet)S(O)_2NR^\bullet_2$, $-N(R^\bullet)S(O)_2R^\bullet$, $-N(OR^\bullet)R^\bullet$, $-C(NH)NR^\bullet_2$, $-P(O)_2R^\bullet$, $-P(O)R^\bullet$, $-OP(O)R^\bullet$, $-OP(O)(OR^\bullet)_2$, $SiR^\bullet_3$, $-(C_{1-4}$ straight or branched alkylene) $O-N(R^\bullet)_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^\bullet)_2$.

${}^2\text{C}(\text{O})\text{OR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SH}$, $-(\text{CH}_2)_{0-2}\text{NH}_2$, $-(\text{CH}_2)_{0-2}\text{NHR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{NR}^\bullet_2$, $-\text{NO}_2$, $-\text{SiR}^\bullet_3$, $-\text{OSiR}^\bullet_3$, $-\text{C}(\text{O})\text{SR}^\bullet$, $-(\text{C}_{1-4}$ straight or branched alkylenc) $\text{C}(\text{O})\text{OR}^\bullet$, or $-\text{SSR}^\bullet$.

[0046] Each $\text{R}^\bullet$ is independently selected from C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $\text{R}^\bullet$ is unsubstituted or where preceded by halo is substituted only with one or more halogens; or wherein an optional substituent on a saturated carbon is a divalent substituent independently selected from $=\text{O}$, $=\text{S}$, $=\text{NNR}^\bullet_2$, $=\text{NNHC}(\text{O})\text{R}^\bullet$, $=\text{NNHC}(\text{O})\text{OR}^\bullet$, $=\text{NNHS}(\text{O})_2\text{R}^\bullet$, $=\text{NR}^\bullet$, $=\text{NOR}^\bullet$, $-\text{O}(\text{C}(\text{R}^\bullet_2))_{2-3}\text{O}-$, or $-\text{S}(\text{C}(\text{R}^\bullet_2))_{2-3}\text{S}-$, or a divalent substituent bound to vicinal substitutable carbons of an “optionally substituted” group is $-\text{O}(\text{CR}^\bullet_2)_{2-3}\text{O}-$, wherein each independent occurrence of $\text{R}^\bullet$ is selected from hydrogen, C_{1-6} aliphatic or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0047] When $\text{R}^\bullet$ is C_{1-6} aliphatic, $\text{R}^\bullet$ is optionally substituted with halogen, $-\text{R}^\bullet$, $-(\text{haloR}^\bullet)$, $-\text{OH}$, $-\text{OR}^\bullet$, $-\text{O}(\text{haloR}^\bullet)$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^\bullet$, $-\text{NH}_2$, $-\text{NHR}^\bullet$, $-\text{NR}^\bullet_2$, or $-\text{NO}_2$, wherein each $\text{R}^\bullet$ is independently selected from C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $\text{R}^\bullet$ is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0048] An optional substituent on a substitutable nitrogen is independently $-\text{R}^\dagger$, $-\text{NR}^\dagger_2$, $-\text{C}(\text{O})\text{R}^\dagger$, $-\text{C}(\text{O})\text{OR}^\dagger$, $-\text{C}(\text{O})\text{C}(\text{O})\text{R}^\dagger$, $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{R}^\dagger$, $-\text{S}(\text{O})_2\text{R}^\dagger$, $-\text{S}(\text{O})_2\text{NR}^\dagger_2$, $-\text{C}(\text{S})\text{NR}^\dagger_2$, $-\text{C}(\text{NH})\text{NR}^\dagger_2$, or $-\text{N}(\text{R}^\dagger)\text{S}(\text{O})_2\text{R}^\dagger$; wherein each $\text{R}^\dagger$ is independently hydrogen, C_{1-6} aliphatic, unsubstituted $-\text{OPh}$, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, two independent occurrences of $\text{R}^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein when $\text{R}^\dagger$ is C_{1-6} aliphatic, $\text{R}^\dagger$ is optionally substituted with halogen, $-\text{R}^\bullet$, $-(\text{haloR}^\bullet)$, $-\text{OH}$, $-\text{OR}^\bullet$, $-\text{O}(\text{haloR}^\bullet)$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^\bullet$, $-\text{NH}_2$, $-\text{NHR}^\bullet$, $-\text{NR}^\bullet_2$, or $-\text{NO}_2$, wherein each $\text{R}^\bullet$ is independently selected from C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from

nitrogen, oxygen, or sulfur, and wherein each R[•] is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0049] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[0050] Further, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al.*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al.*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al.*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference.

[0051] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0052] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. One embodiment of the invention pertains to compounds having the natural distribution of isotopes, e.g., a structure depicted herein wherein the compound(s) have the natural distribution of isotopes.

[0053] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Alternatively, a particular enantiomer of a compound of the present invention may be prepared by asymmetric synthesis. Still further, where the molecule contains a basic functional group (such as amino) or an acidic functional group (such as carboxylic acid) diastereomeric salts are formed with an appropriate optically-

active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means known in the art, and subsequent recovery of the pure enantiomers.

[0054] Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. Chiral center(s) in a compound of the present invention can have the *S* or *R* configuration as defined by the *IUPAC* 1974 Recommendations. Further, to the extent a compound described herein may exist as a atropisomer (*e.g.*, substituted biaryls), all forms of such atropisomer are considered part of this invention.

[0055] Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name, and an ambiguity exists between the structure and the name, the structure predominates. It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

[0056] The terms “a” and “an” as used herein mean “one or more” and include the plural unless the context is inappropriate.

[0057] The term “alkyl” refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C₁-C₁₂ alkyl, C₁-C₁₀ alkyl, and C₁-C₆ alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

[0058] The term “cycloalkyl” refers to a monovalent saturated cyclic, bicyclic, or bridged cyclic (*e.g.*, adamantyl) hydrocarbon group of 3-12, 3-8, 4-8, or 4-6 carbons, referred to herein, *e.g.*, as “C₃-C₆ cycloalkyl,” derived from a cycloalkane. Exemplary cycloalkyl groups include cyclohexyl, cyclopentyl, cyclobutyl, and cyclopropyl. The term “cycloalkylene” refers to a bivalent cycloalkyl group.

[0059] The term “haloalkyl” refers to an alkyl group that is substituted with at least one halogen. Exemplary haloalkyl groups include -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CF₂CF₃, and the like. The term “haloalkylene” refers to a bivalent haloalkyl group.

[0060] The term “hydroxyalkyl” refers to an alkyl group that is substituted with at least one hydroxyl. Exemplary hydroxyalkyl groups include -CH₂CH₂OH, -C(H)(OH)CH₃, -CH₂C(H)(OH)CH₂CH₂OH, and the like.

[0061] The terms “alkenyl” and “alkynyl” are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

[0062] The term “carbocyclylene” refers to a multivalent carbocyclyl group having the appropriate number of open valences to account for groups attached to it. For example, “carbocyclylene” is a bivalent carbocyclyl group when it has two groups attached to it; “carbocyclylene” is a trivalent carbocyclyl group when it has three groups attached to it.

[0063] The terms “alkoxyl” or “alkoxy” are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, *tert*-butoxy and the like. The term “haloalkoxyl” refers to an alkoxyl group that is substituted with at least one halogen. Exemplary haloalkoxyl groups include -OCH₂F, -OCHF₂, -OCF₃, -OCH₂CF₃, -OCF₂CF₃, and the like. The term “hydroxyalkoxyl” refers to an alkoxyl group that is substituted with at least one hydroxyl. Exemplary hydroxyalkoxyl groups include -OCH₂CH₂OH, -OCH₂C(H)(OH)CH₂CH₂OH, and the like. The term “alkoxyylene” refers to a bivalent alkoxyl group.

[0064] The term “oxo” is art-recognized and refers to a “=O” substituent. For example, a cyclopentane substituted with an oxo group is cyclopentanone.

[0065] The symbol “” indicates a point of attachment.

[0066] When any substituent or variable occurs more than one time in any constituent or the compound of the invention, its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise indicated.

[0067] One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is

intended that the invention embrace both solvated and unsolvated forms. “Solvate” means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. “Solvate” encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanولات, methanولات, and the like. “Hydrate” is a solvate wherein the solvent molecule is H₂O.

[0068] As used herein, the terms “subject” and “patient” are used interchangeably and refer to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and, most preferably, includes humans.

[0069] As used herein, the term “effective amount” refers to the amount of a compound sufficient to effect beneficial or desired results (*e.g.*, a therapeutic, ameliorative, inhibitory, or preventative result). An effective amount can be administered in one or more administrations, applications, or dosages and is not intended to be limited to a particular formulation or administration route.

[0070] As used herein, the term “treating” includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof. In some embodiments, treatment can be administered after one or more symptoms have developed. In other embodiments, treatment can be administered in the absence of symptoms. For example, treatment can be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment can also be continued after symptoms have resolved, for example, to prevent or delay their recurrence.

[0071] As used herein, the term “pharmaceutical composition” refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0072] As used herein, the term “pharmaceutically acceptable carrier” refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, *see e.g.*, Martin, Remington’s Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0073] For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[0074] In addition, when a compound of the invention contains both a basic moiety (such as, but not limited to, a pyridine or imidazole) and an acidic moiety (such as, but not limited to, a carboxylic acid) zwitterions (“inner salts”) may be formed. Such acidic and basic salts used within the scope of the invention are pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts. Such salts of the compounds of the invention may be formed, for example, by reacting a compound of the invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0075] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

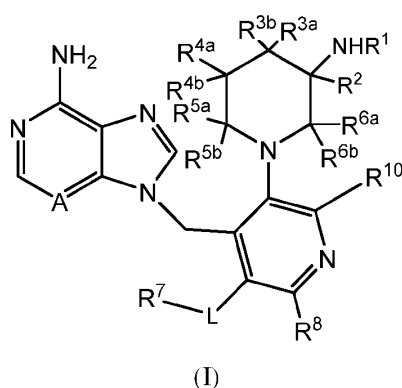
[0076] As a general matter, compositions specifying a percentage are by weight unless otherwise specified.

II. Therapeutic Applications

[0077] The present invention provides methods and compositions for using a piperidinyl-methyl-purineamine nuclear SET domain-containing protein 2 (NSD2) inhibitor to treat cancer,

such as combination therapies to treat cancer. One aspect of the invention provides a method of treating cancer, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount of a first therapeutic agent described herein and a second therapeutic agent described herein to treat the cancer.

[0078] In a more specific embodiment, the invention provides a method of treating cancer, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount of a first therapeutic agent and a second therapeutic agent to treat the cancer, wherein the first therapeutic agent is a compound of Formula I:



or a pharmaceutically acceptable salt thereof; wherein:

A is N or CR⁹ wherein R⁹ is hydrogen or halo;

L is a bond or C₁₋₄ alkylene;

R¹ is H; or

R¹ and R² together with NH forms a 5-8 membered heterocyclyl containing 1-2 heteroatoms selected from N, O and S as ring members; wherein said 5-8 membered heterocyclyl is unsubstituted or substituted by an oxo substituent;

R² is selected from the group consisting of:

(i) hydrogen, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -hydroxyC₁₋₆ alkylene, -hydroxyhaloC₁₋₆ alkylene, -C₁₋₆alkoxyC₁₋₆alkylene, -haloC₁₋₆ alkoxyC₁₋₆ alkylene or -C₃₋₈ cycloalkoxy(C₁₋₆ alkyl);

(ii) cyano; -cyanoC₁₋₆ alkylene; -C₁₋₆ alkylthioC₁₋₆alkyl; -C₂₋₆ alkenyl; -haloC₂₋₆ alkenyl; -C₂₋₆ alkynyl; -C₁₋₄ alkylSOC₁₋₄alkyl; -C₁₋₄ alkylSO₂C₁₋₄alkyl; -SO₂R⁸ or -C(C₁₋₄ alkyl)=N-O(C₁₋₄ alkyl);

(iii) $-\text{C}_{1-4}\text{alkylcarbonyl}$; $-(\text{CR}^a\text{R}^b)_p-\text{C}(=\text{O})-\text{OR}^{10}$; or $-\text{C}(=\text{O})-(\text{CR}^a\text{R}^b)_q\text{R}^{11}$; wherein R^{11} is C_{3-7} cycloalkyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl, each of which is independently unsubstituted or substituted with C_{1-6} alkyl or C_{1-6} alkoxy;

(iv) $-(\text{CR}^a\text{R}^b)_r-\text{C}(=\text{O})-\text{NR}^{12}\text{R}^{13}$ wherein R^{12} is hydrogen or C_{1-6} alkyl; R^{13} is hydrogen, $-\text{C}_{1-6}$ alkyl or a 5-6 membered heterocyclic ring; or R^{12} and R^{13} together form a 5-6 membered heterocyclic ring; wherein said 5-6 membered heterocyclic ring is unsubstituted or substituted with C_{1-4} alkyl;

(v) 5-6 membered heterocyclyl $\text{C}_{0-6}\text{alkyl}$ or 5-6 membered heterocyclyl(halo C_{1-4} alkyl) wherein each said heterocyclyl radical is unsubstituted or substituted by oxo; and

(vi) 5-9 membered heteroaryl $\text{C}_{0-6}\text{alkyl}$ or 5-9 membered heteroaryl(halo C_{1-4} alkyl), wherein each said heteroaryl radical is unsubstituted or substituted by $-\text{C}_{1-4}$ alkyl, $-\text{haloC}_{1-4}$ alkyl, $-\text{hydroxyC}_{1-4}$ alkylene, $-\text{C}_{1-4}$ alkoxy, $-\text{haloC}_{1-4}$ alkoxy, halo, hydroxy, cyano, oxido, $-\text{aminocarbonylC}_{0-6}\text{alkyl}$, $-\text{C}_{1-4}\text{alkylaminocarbonylC}_{0-6}\text{alkyl}$, $-\text{diC}_{1-4}\text{alkylaminocarbonylC}_{0-6}\text{alkyl}$ or $-\text{C}_{3-7}$ cycloalkyl;

R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{5a} , R^{5b} , R^{6a} and R^{6b} are independently hydrogen, halo, cyano, hydroxyl, $-\text{C}_{1-6}$ alkyl, $-\text{haloC}_{1-6}$ alkyl, $-\text{hydroxyC}_{1-6}$ alkylene, $-\text{C}_{1-6}$ alkoxy, $-\text{C}_{1-6}\text{alkoxyC}_{1-6}\text{alkylene}$, $-\text{haloC}_{1-6}\text{alkoxyC}_{1-6}\text{alkylene}$, $-\text{hydroxyhaloC}_{1-6}$ alkylene, aryl, $-\text{C}(=\text{O})-\text{OR}^{14}$ or $-(\text{CR}^a\text{R}^b)_s-\text{C}(=\text{O})-\text{NR}^{15}\text{R}^{16}$; or

R^{3a} and R^{3b} , R^{4a} and R^{4b} , R^{5a} and R^{5b} or R^{6a} and R^{6b} forms an oxo substituent;

R^7 is H, $-\text{C}_{1-4}$ alkoxy, halo or C_{1-4} alkyl; or 3-8 membered heterocyclyl, which is unsubstituted or substituted by halo;

R^8 is C_{3-8} cycloalkyl(C_{0-6} alkyl); 4-6 membered heterocyclyl $\text{C}_{0-6}\text{alkyl}$ comprising 1-3 heteroatoms selected from N, O and S; aryl or 5-9 membered heteroaryl $\text{C}_{0-6}\text{alkyl}$ comprising 1-3 heteroatoms selected from N, O and S; wherein R^8 is unsubstituted or substituted by 1-3 R^{17} ;

R^{17} is halo, hydroxy, cyano, $-\text{C}_{1-6}$ alkyl, $-\text{haloC}_{1-6}$ alkyl, $-\text{C}_{1-6}$ alkoxy, $-\text{haloC}_{1-6}$ alkoxy, $-\text{NR}^a\text{C}(=\text{O})\text{CR}^c=\text{C}(\text{R}^c)_2$ or $-(\text{CR}^a\text{R}^b)_t-\text{NR}^a-\text{C}(=\text{O})-\text{R}^{18}$;

R^a , R^b , R^c , R^{10} , R^{14} , R^{15} and R^{16} are independently hydrogen or $-\text{C}_{1-4}$ alkyl;

R^{18} is $-\text{C}_{1-4}$ alkyl or $-\text{C}_{1-4}$ haloalkyl; and

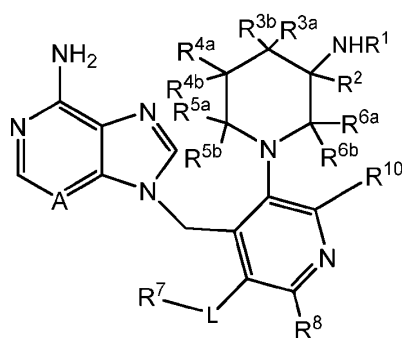
p, q, r, s and t are independently 0-4; and

the second therapeutic agent is (i) daratumumab, isatuximab, idecabtegene vicleucel, ciltacabtegene autoleucel, or belantamab mafodotin-blmf, (ii) bortezomib, carfilzomib, ixazomib,

thalidomide, lenalidomide, pomalidomide, mezigdomide, iberdomide, selinexor, binimetinib, cobimetinib, selumetinib, refametinib, PD-0325901, or ROS126766, or a pharmaceutically acceptable salt thereof, (iii) dacomitinib, mobercitinib, neratinib, osimertinib, or vandetenib, or a pharmaceutically acceptable salt thereof, (iv) a bispecific antibody that binds CD3, (v) a tagged antibody, (vi) a chimeric antigen receptor (CAR) T-cell therapy cell therapy or a natural killer (NK) cell therapy, (vii) a natural killer cell engager, (viii) a KRAS inhibitor, (ix) an immune checkpoint inhibitor, (x) an FGFR3 inhibitor, (xi) an androgen receptor inhibitor, (xii) a BCL-2, BCLXL, or MCL1 inhibitor, (xiii) PARP inhibitor, (xiv) an androgen receptor degrader, or (xv) a radioligand therapy agent.

[0079] The method may be further characterized according to, for example, the identity of the cancer to be treated, the identity of the first therapeutic agent, the identity of the second therapeutic agent, and identity of the subject to be treated. These and other features are described in more detail below. For example, in certain embodiments, the method comprises administering to the subject a therapeutically effective amount of (i) a compound of Formula I or a pharmaceutically acceptable salt thereof, and (ii) carfilzomib or a pharmaceutically acceptable salt thereof. In certain embodiments, the method comprises administering to the subject a therapeutically effective amount of (i) a compound of Formula I or a pharmaceutically acceptable salt thereof, and (ii) mezigdomide or a pharmaceutically acceptable salt thereof. In certain embodiments, the method comprises administering to the subject a therapeutically effective amount of (i) a compound of Formula I or a pharmaceutically acceptable salt thereof, (ii) carfilzomib or a pharmaceutically acceptable salt thereof, and (iii) mezigdomide or a pharmaceutically acceptable salt thereof.

[0080] Another aspect of the invention provides a method of treating cancer in subject that has previously received one or more prior anti-cancer therapies, wherein the method comprises administering to the subject in need thereof a therapeutically effective amount of a compound of Formula I to treat the cancer, wherein Formula I is represented by:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

A is N or CR⁹ wherein R⁹ is hydrogen or halo;

L is a bond or C₁₋₄ alkylene;

R¹ is H; or

R¹ and R² together with NH forms a 5-8 membered heterocyclyl containing 1-2 heteroatoms selected from N, O and S as ring members; wherein said 5-8 membered heterocyclyl is unsubstituted or substituted by an oxo substituent;

R² is selected from the group consisting of:

(i) hydrogen, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -hydroxyC₁₋₆ alkylene, -hydroxyhaloC₁₋₆ alkylene, -C₁₋₆alkoxyC₁₋₆alkylene, -haloC₁₋₆ alkoxyC₁₋₆ alkylene or -C₃₋₈ cycloalkoxy(C₁₋₆ alkyl);

(ii) cyano; -cyanoC₁₋₆ alkylene; -C₁₋₆ alkylthioC₁₋₆alkyl; -C₂₋₆ alkenyl; -haloC₂₋₆ alkenyl; -C₂₋₆ alkynyl; -C₁₋₄ alkylSOC₁₋₄alkyl; -C₁₋₄ alkylSO₂C₁₋₄alkyl; -SO₂R⁸ or -C(C₁₋₄ alkyl)=N-O(C₁₋₄ alkyl);

(iii) -C₁₋₄alkylcarbonyl; -(CR^aR^b)_p-C(=O)-OR¹⁰; or -C(=O)-(CR^aR^b)_qR¹¹; wherein R¹¹ is C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl, each of which is independently unsubstituted or substituted with C₁₋₆ alkyl or C₁₋₆ alkoxy;

(iv) -(CR^aR^b)_r-C(=O)-NR¹²R¹³ wherein R¹² is hydrogen or C₁₋₆ alkyl; R¹³ is hydrogen, -C₁₋₆ alkyl or a 5-6 membered heterocyclic ring; or R¹² and R¹³ together form a 5-6 membered heterocyclic ring; wherein said 5-6 membered heterocyclic ring is unsubstituted or substituted with C₁₋₄ alkyl;

(v) 5-6 membered heterocyclylC₀₋₆alkyl or 5-6 membered heterocyclyl(haloC₁₋₄ alkyl) wherein each said heterocyclyl radical is unsubstituted or substituted by oxo; and

(vi) 5-9 membered heteroarylC₀₋₆alkyl or 5-9 membered heteroaryl(haloC₁₋₄alkyl), wherein each said heteroaryl radical is unsubstituted or substituted by -C₁₋₄ alkyl, -haloC₁₋₄ alkyl, -hydroxyC₁₋₄ alkylene, -C₁₋₄ alkoxy, -haloC₁₋₄ alkoxy, halo, hydroxy, cyano, oxido, -aminocarbonylC₀₋₆alkyl, -C₁₋₄alkylaminocarbonylC₀₋₆alkyl, -diC₁₋₄alkylaminocarbonylC₀₋₆alkyl or -C₃₋₇ cycloalkyl;

R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{6a} and R^{6b} are independently hydrogen, halo, cyano, hydroxyl, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -hydroxyC₁₋₆ alkylene, -C₁₋₆ alkoxy, -C₁₋₆alkoxyC₁₋₆alkylene, -haloC₁₋₆ alkoxyC₁₋₆ alkylene, -hydroxyhaloC₁₋₆ alkylene, aryl, -C(=O)-OR¹⁴ or -(CR^aR^b)_s-C(=O)-NR¹⁵R¹⁶; or

R^{3a} and R^{3b}, R^{4a} and R^{4b}, R^{5a} and R^{5b} or R^{6a} and R^{6b} forms an oxo substituent;

R⁷ is H, -C₁₋₄ alkoxy, halo or C₁₋₄ alkyl; or 3-8 membered heterocyclyl, which is unsubstituted or substituted by halo;

R⁸ is C₃₋₈ cycloalkyl(C₀₋₆ alkyl); 4-6 membered heterocyclylC₀₋₆alkyl comprising 1-3 heteroatoms selected from N, O and S; aryl or 5-9 membered heteroarylC₀₋₆alkyl comprising 1-3 heteroatoms selected from N, O and S; wherein R⁸ is unsubstituted or substituted by 1-3 R¹⁷;

R¹⁷ is halo, hydroxy, cyano, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -C₁₋₆ alkoxy, -haloC₁₋₆ alkoxy, -NR^aC(=O)CR^c=C(R^c)₂ or -(CR^aR^b)_t-NR^a-C(=O)-R¹⁸;

R^a, R^b, R^c, R¹⁰, R¹⁴, R¹⁵ and R¹⁶ are independently hydrogen or -C₁₋₄ alkyl;

R¹⁸ is -C₁₋₄ alkyl or -C₁₋₄ haloalkyl; and

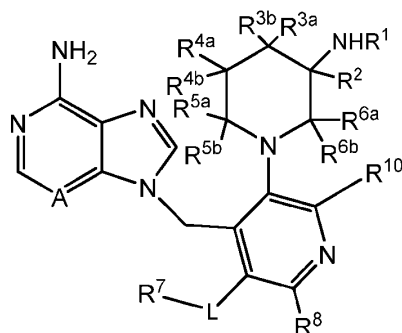
p, q, r, s and t are independently 0-4.

[0081] The method may be further characterized according to, for example, the identity of the cancer to be treated, the identity of the compound of Formula I, the identity of the prior anti-cancer agent, and identity of the subject to be treated. These and other features are described in more detail below. For example, in certain embodiments, at least one of the prior anti-cancer therapies is a proteasome inhibitor, immunomodulatory drug, immunotherapy antibody, CAR-T therapy, antibody-drug conjugate, bispecific antibody, or MEK inhibitor. In certain embodiments, at least one of the prior anti-cancer therapies is carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, daratumumab, isatuximab, idecabtegene vicleucel, ciltacabtegene autoleucel, belantamab mafodotin-blmf, selinexor, binimetinib, cobimetinib, selumetinib, sotorasib, teclistamab, elrantamab, or talquetamab, or a pharmaceutically acceptable salt thereof.

[0082] In certain embodiments, the subject has previously received one prior anti-cancer therapy selected from a proteasome inhibitor, immunomodulatory drug, immunotherapy antibody, CAR-T therapy, antibody therapy, antibody-drug conjugate, XPO1 inhibitor, EGFR inhibitor, KRAS inhibitor, and MEK inhibitor. In certain embodiments, the subject has previously received one prior anti-cancer therapy selected from carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, daratumumab, elotuzumab, isatuximab, idecabtegene vicleucel, ciltacabtegene autoleucel, belantamab mafodotin-blmf, selinexor, teclistamab, elrantamab, talquetamab, binimetinib, cobimetinib, selumetinib, sotorasib, osimertinib, erlotinib, gefitinib, dacomitinib, adagrasib, mezigdomide, and iberdomide, or a pharmaceutically acceptable salt thereof.

[0083] In certain embodiments, the subject has previously received at least two anti-cancer therapies. In certain embodiments, the subject has previously received at least three anti-cancer therapies. In certain embodiments, the subject has previously received at least four anti-cancer therapies.

[0084] Another aspect of the invention provides a method of treating cancer in subject, wherein the method comprises administering to the subject in need thereof a therapeutically effective amount of a compound of Formula I to treat the cancer, wherein Formula I is represented by:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

A is N or CR⁹ wherein R⁹ is hydrogen or halo;

L is a bond or C₁₋₄ alkylene;

R¹ is H; or

R¹ and R² together with NH forms a 5-8 membered heterocyclyl containing 1-2 heteroatoms selected from N, O and S as ring members; wherein said 5-8 membered heterocyclyl is unsubstituted or substituted by an oxo substituent;

R² is selected from the group consisting of:

(i) hydrogen, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -hydroxyC₁₋₆ alkylene, -hydroxyhaloC₁₋₆ alkylene, -C₁₋₆alkoxyC₁₋₆alkylene, -haloC₁₋₆alkoxyC₁₋₆alkylene or -C₃₋₈ cycloalkoxy(C₁₋₆ alkyl);

(ii) cyano; -cyanoC₁₋₆ alkylene; -C₁₋₆ alkylthioC₁₋₆alkyl; -C₂₋₆ alkenyl; -haloC₂₋₆ alkenyl; -C₂₋₆ alkynyl; -C₁₋₄ alkylSOC₁₋₄alkyl; -C₁₋₄ alkylSO₂C₁₋₄alkyl; -SO₂R⁸ or -C(C₁₋₄ alkyl)=N-O(C₁₋₄ alkyl);

(iii) -C₁₋₄alkylcarbonyl; -(CR^aR^b)_p-C(=O)-OR¹⁰; or -C(=O)-(CR^aR^b)_qR¹¹; wherein R¹¹ is C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl, each of which is independently unsubstituted or substituted with C₁₋₆ alkyl or C₁₋₆ alkoxy;

(iv) -(CR^aR^b)_r-C(=O)-NR¹²R¹³ wherein R¹² is hydrogen or C₁₋₆ alkyl; R¹³ is hydrogen, -C₁₋₆ alkyl or a 5-6 membered heterocyclic ring; or R¹² and R¹³ together form a 5-6 membered heterocyclic ring; wherein said 5-6 membered heterocyclic ring is unsubstituted or substituted with C₁₋₄ alkyl;

(v) 5-6 membered heterocyclylC₀₋₆alkyl or 5-6 membered heterocyclyl(haloC₁₋₄ alkyl) wherein each said heterocyclyl radical is unsubstituted or substituted by oxo; and

(vi) 5-9 membered heteroarylC₀₋₆alkyl or 5-9 membered heteroaryl(haloC₁₋₄alkyl), wherein each said heteroaryl radical is unsubstituted or substituted by -C₁₋₄ alkyl, -haloC₁₋₄ alkyl, -hydroxyC₁₋₄ alkylene, -C₁₋₄ alkoxy, -haloC₁₋₄ alkoxy, halo, hydroxy, cyano, oxido, -aminocarbonylC₀₋₆alkyl, -C₁₋₄alkylaminocarbonylC₀₋₆alkyl, -diC₁₋₄alkylaminocarbonylC₀₋₆alkyl or -C₃₋₇ cycloalkyl;

R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{6a} and R^{6b} are independently hydrogen, halo, cyano, hydroxyl, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -hydroxyC₁₋₆ alkylene, -C₁₋₆ alkoxy, -C₁₋₆alkoxyC₁₋₆alkylene, -haloC₁₋₆alkoxyC₁₋₆alkylene, -hydroxyhaloC₁₋₆ alkylene, aryl, -C(=O)-OR¹⁴ or -(CR^aR^b)_s-C(=O)-NR¹⁵R¹⁶; or

R^{3a} and R^{3b}, R^{4a} and R^{4b}, R^{5a} and R^{5b} or R^{6a} and R^{6b} forms an oxo substituent;

R⁷ is H, -C₁₋₄ alkoxy, halo or C₁₋₄ alkyl; or 3-8 membered heterocyclyl, which is unsubstituted or substituted by halo;

R^8 is C_{3-8} cycloalkyl(C_{0-6} alkyl); 4-6 membered heterocyclyl(C_{0-6} alkyl) comprising 1-3 heteroatoms selected from N, O and S; aryl or 5-9 membered heteroaryl(C_{0-6} alkyl) comprising 1-3 heteroatoms selected from N, O and S; wherein R^8 is unsubstituted or substituted by 1-3 R^{17} ;

R^{17} is halo, hydroxy, cyano, $-C_{1-6}$ alkyl, $-haloC_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-haloC_{1-6}$ alkoxy, $-NR^aC(=O)CR^c=C(R^c)_2$ or $-(CR^aR^b)_t-NR^a-C(=O)-R^{18}$;

R^a , R^b , R^c , R^{10} , R^{14} , R^{15} and R^{16} are independently hydrogen or $-C_{1-4}$ alkyl;

R^{18} is $-C_{1-4}$ alkyl or $-C_{1-4}$ haloalkyl; and

p, q, r, s and t are independently 0-4.

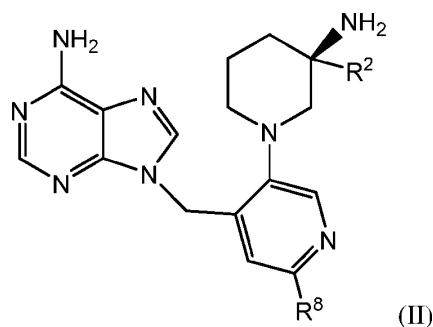
[0085] The method may be further characterized according to, for example, the identity of the cancer to be treated, the identity of the compound of Formula I, and identity of the subject to be treated. For example, in certain embodiments, the compound is a compound of Formula I. In certain embodiments, A is N. In certain embodiments, R^{3a} is hydrogen or halo; and R^{3b} is hydrogen, halo, $-hydroxyl$, $-C_{1-6}$ alkoxy or cyano; or R^{4a} is hydrogen or halo; and R^{4b} is hydrogen, halo, $-C_{1-6}alkoxyC_{1-6}alkylene$, $-C_{1-6}$ alkyl or $-haloC_{1-6}$ alkyl; or R^{5a} is hydrogen and R^{5b} is hydrogen or $-C_{1-6}$ alkyl; or R^{5a} and R^{5b} together form an oxo substituent.

[0086] In certain embodiments, R^{6a} is hydrogen or halo; R^{6b} is hydrogen, $-haloC_{1-6}$ alkoxy C_{1-6} alkylene, $-hydroxyc_{1-6}$ alkylene, $-hydroxyhaloC_{1-6}$ alkylene, carboxyl, phenyl or $-(CR^aR^b)_t-C(O)-NR^{15}R^{16}$; R^a , R^b , R^{15} and R^{16} are independently hydrogen or $-C_{1-4}$ alkyl; and t is 0-1; or R^{6a} and R^{6b} together form an oxo substituent.

[0087] In certain embodiments, R^7 is H, $-C_{1-4}$ alkoxy or halo.

[0088] In certain embodiments, R^1 , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{5a} , R^{5b} , R^{6a} , R^{6b} and R^7 are hydrogen.

[0089] In certain embodiments, said compound is a compound of Formula (II):

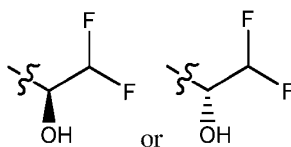


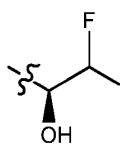
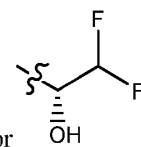
or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof.

[0090] In certain embodiments, R^2 is $-C_{1-6}$ alkyl, $-\text{halo}C_{1-6}$ alkyl, $-\text{hydroxy}C_{1-6}$ alkylene, $-\text{hydroxyhalo}C_{1-6}$ alkylene, $-C_{1-6}\text{alkoxy}C_{1-6}\text{alkylene}$, $-\text{halo}C_{1-6}\text{alkoxy}C_{1-6}\text{alkylene}$ or $-C_{3-8}$ cycloalkoxy(C_{1-6} alkyl).

[0091] In certain embodiments, R^2 is 2,2-difluoroethyl; 2-methyl-propan-1-olyl; ethan-1-olyl; 2,2-difluoroethan-1-olyl; 2-fluoroethan-1-olyl; 2,2,2-trifluoroethan-1-olyl; difluoromethoxyl; or 2,2,2-trifluoroethoxyl.

[0092] In certain embodiments, R^2 is 2,2-difluoroethyl; 2-methyl-propan-1-olyl; ethan-1-olyl; 2,2-difluoroethan-1-olyl; 2-fluoroethan-1-olyl; 2,2,2-trifluoroethan-1-olyl; difluoromethoxyl; or 2,2,2-trifluoroethoxyl.



[0093] In certain embodiments, R^2 is  or .

[0094] In certain embodiments, R^8 is phenyl substituted with 1-3 R^{17} ; wherein R^{17} is halo, hydroxy, cyano, $-C_{1-6}$ alkyl, $-\text{halo}C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-\text{halo}C_{1-6}$ alkoxy, $-\text{NR}^d\text{C}(\text{O})\text{CR}^d=\text{C}(\text{R}^d)_2$ or $-(\text{CR}^a\text{R}^b)_t-\text{NR}^d-\text{C}(\text{O})-\text{R}^{18}$; R^a , R^b and R^d are independently hydrogen or $-C_{1-4}$ alkyl; R^{18} is C_{1-4} haloalkyl; and t is 0-1.

[0095] In certain embodiments, R^8 is phenyl substituted with 1-3 R^{17} ;

R^{17} is halo, hydroxy, cyano, $-C_{1-6}$ alkyl, $-\text{halo}C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-\text{halo}C_{1-6}$ alkoxy, $-\text{NR}^d\text{C}(\text{O})\text{CR}^d=\text{C}(\text{R}^d)_2$ or $-(\text{CR}^a\text{R}^b)_t-\text{NR}^d-\text{C}(\text{O})-\text{R}^{18}$;

R^a , R^b and R^d are independently hydrogen or $-C_{1-4}$ alkyl;

R^{18} is C_{1-4} haloalkyl; and

t is 0-1.

[0096] In certain embodiments, R^8 is phenyl substituted with 1-3 R^{17} ; and R^{17} is halo, hydroxy, $-C_{1-6}$ alkyl, $-\text{halo}C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy or $-\text{halo}C_{1-6}$ alkoxy.

[0097] In certain embodiments, R^8 is phenyl substituted with 1-3 R^{17} ; and R^{17} is halo, hydroxy, $-C_{1-6}$ alkyl, $-\text{halo}C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy or $-\text{halo}C_{1-6}$ alkoxy.

[0098] The methods may be further characterized according to, for example, the identity of the cancer to be treated, the identity of the compound of Formula I, and identity of the subject to be treated. These and other features are described in more detail below.

Cancer

[0099] In certain embodiments, the cancer is a solid tumor. In certain embodiments, the cancer is a melanoma, carcinoma, neuroblastoma, sarcoma, leukemia, or lymphoma. In certain embodiments, the cancer is a melanoma, carcinoma, or blastoma. In certain embodiments, the cancer is a melanoma. In certain embodiments, the cancer is a carcinoma. In certain embodiments, the cancer is an adenocarcinoma. In certain embodiments, the cancer is a blastoma.

[0100] In certain embodiments, the cancer is leukemia. In certain embodiments, the cancer is lymphoma. In certain embodiments, the cancer is acute lymphoblastic leukemia, mantle cell lymphoma, or diffuse large B cell lymphoma.

[0101] In certain embodiments, the cancer is breast cancer, lung cancer, pancreatic cancer, cervical cancer, colorectal cancer, prostate cancer, gastric cancer, skin cancer, liver cancer, bile duct cancer, or nervous system cancer. In certain embodiments, the cancer is breast cancer. In certain embodiments, the cancer is lung cancer. In certain embodiments, the cancer is pancreatic cancer. In certain embodiments, the cancer is cervical cancer. In certain embodiments, the cancer is colorectal cancer. In certain embodiments, the cancer is prostate cancer. In certain embodiments, the cancer is gastric cancer. In certain embodiments, the cancer is skin cancer. In certain embodiments, the cancer is liver cancer. In certain embodiments, the cancer is bile duct cancer. In certain embodiments, the cancer is nervous system cancer.

[0102] In certain embodiments, the cancer is breast adenocarcinoma, lung adenocarcinoma, pancreatic adenocarcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, prostate adenocarcinoma, gastric adenocarcinoma, melanoma, lung squamous cell carcinoma, hepatocellular carcinoma, cholangiocarcinoma, glioblastoma, neuroblastoma, or multiple myeloma. In certain embodiments, the cancer is breast adenocarcinoma. In certain embodiments, the cancer is lung adenocarcinoma. In certain embodiments, the cancer is pancreatic adenocarcinoma. In certain embodiments, the cancer is cervical adenocarcinoma. In certain embodiments, the cancer is prostate adenocarcinoma. In certain embodiments, the cancer is gastric adenocarcinoma.

[0103] In certain embodiments, the cancer is melanoma.

[0104] In certain embodiments, the cancer is lung squamous cell carcinoma, hepatocellular carcinoma, or cholangiocarcinoma. In certain embodiments, the cancer is lung squamous cell

carcinoma. In certain embodiments, the cancer is hepatocellular carcinoma. In certain embodiments, the cancer is cholangiocarcinoma.

[0105] In certain embodiments, the cancer is glioblastoma or neuroblastoma. In certain embodiments, the cancer is glioblastoma. In certain embodiments, the cancer is neuroblastoma.

[0106] In certain embodiments, the cancer is lung cancer, pancreatic cancer, or colorectal cancer. In certain embodiments, the cancer is non-small cell lung cancer, pancreatic cancer, or colorectal cancer. In certain embodiments, the cancer is lung cancer. In certain embodiments, the cancer is non-small cell lung cancer.

[0107] In certain embodiments, the cancer is non-small cell lung cancer. In certain embodiments, the cancer is multiple myeloma. In certain embodiments, the cancer is refractory. In certain embodiments, the cancer is a relapsed cancer. In certain embodiments, the cancer is relapsed, refractory multiple myeloma.

[0108] In certain embodiments, the cancer has a RAS mutation. In certain embodiments, the cancer has a KRAS G12c mutation.

[0109] In certain embodiments, the cancer is a leukemia (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (e.g., Hodgkin's disease or non-Hodgkin's disease), Waldenstrom's macroglobulinemia, multiple myeloma, heavy chain disease, or a solid tumor such as a sarcoma or carcinoma (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, glioblastoma

multiforme (GBM, also known as glioblastoma), medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, neurofibrosarcoma, meningioma, melanoma, neuroblastoma, and retinoblastoma).

[0110] In some embodiments, the cancer is glioma, astrocytoma, glioblastoma multiforme (GBM, also known as glioblastoma), medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, neurofibrosarcoma, meningioma, melanoma, neuroblastoma, or retinoblastoma.

[0111] In some embodiments, the cancer is acoustic neuroma, astrocytoma (e.g. Grade I – Pilocytic Astrocytoma, Grade II – Low-grade Astrocytoma, Grade III – Anaplastic Astrocytoma, or Grade IV – Glioblastoma (GBM)), chordoma, CNS lymphoma, craniopharyngioma, brain stem glioma, ependymoma, mixed glioma, optic nerve glioma, subependymoma, medulloblastoma, meningioma, metastatic brain tumor, oligodendroglioma, pituitary tumors, primitive neuroectodermal (PNET) tumor, or schwannoma. In some embodiments, the cancer is a type found more commonly in children than adults, such as brain stem glioma, craniopharyngioma, ependymoma, juvenile pilocytic astrocytoma (JPA), medulloblastoma, optic nerve glioma, pineal tumor, primitive neuroectodermal tumors (PNET), or rhabdoid tumor.

[0112] In some embodiments, the cancer is mesothelioma, hepatobiliary (hepatic and biliary duct), bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal, and duodenal), uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, testicular cancer, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, non-Hodgkins's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, multiple myeloma, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma, or a combination of one or more of the foregoing cancers.

[0113] In some embodiments, the cancer is hepatocellular carcinoma, ovarian cancer, ovarian epithelial cancer, fallopian tube cancer, papillary serous cystadenocarcinoma, uterine papillary serous carcinoma (UPSC), prostate cancer, testicular cancer, gallbladder cancer, hepatocholangiocarcinoma, soft tissue and bone synovial sarcoma, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, Ewing sarcoma, anaplastic thyroid cancer, adrenocortical adenoma, pancreatic cancer, pancreatic adenocarcinoma, gastrointestinal/stomach (GIST) cancer, lymphoma, squamous cell carcinoma of the head and neck (SCCHN), salivary gland cancer, glioma, or brain cancer, neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST), Waldenstrom's macroglobulinemia, or medulloblastoma.

[0114] In some embodiments, the cancer is hepatocellular carcinoma (HCC), hepatoblastoma, colon cancer, rectal cancer, ovarian cancer, ovarian epithelial cancer, fallopian tube cancer, papillary serous cystadenocarcinoma, uterine papillary serous carcinoma (UPSC), hepatocholangiocarcinoma, soft tissue and bone synovial sarcoma, rhabdomyosarcoma, osteosarcoma, anaplastic thyroid cancer, adrenocortical adenoma, pancreatic cancer, pancreatic adenocarcinoma, glioma, neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST), Waldenstrom's macroglobulinemia, or medulloblastoma.

[0115] In some embodiments, the cancer is selected from renal cell carcinoma, or kidney cancer; hepatocellular carcinoma (HCC) or hepatoblastoma, or liver cancer; melanoma; breast cancer; colorectal carcinoma, or colorectal cancer; colon cancer; rectal cancer; anal cancer; lung cancer, such as non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC); ovarian cancer, ovarian epithelial cancer, ovarian carcinoma, or fallopian tube cancer; papillary serous cystadenocarcinoma or uterine papillary serous carcinoma (UPSC); prostate cancer; testicular cancer; gallbladder cancer; hepatocholangiocarcinoma; soft tissue and bone synovial sarcoma; rhabdomyosarcoma; osteosarcoma; chondrosarcoma; Ewing sarcoma; anaplastic thyroid cancer; adrenocortical carcinoma; pancreatic cancer; or pancreatic adenocarcinoma; gastrointestinal/stomach (GIST) cancer; lymphoma; squamous cell carcinoma of the head and neck (SCCHN); salivary gland cancer; glioma, or brain cancer; neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST); Waldenstrom's macroglobulinemia; and medulloblastoma.

[0116] In some embodiments, the cancer is renal cell carcinoma, hepatocellular carcinoma (HCC), hepatoblastoma, colorectal carcinoma, colorectal cancer, colon cancer, rectal cancer, anal cancer, ovarian cancer, ovarian epithelial cancer, ovarian carcinoma, fallopian tube cancer, papillary serous cystadenocarcinoma, uterine papillary serous carcinoma (UPSC), hepatocholangiocarcinoma, soft tissue and bone synovial sarcoma, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, anaplastic thyroid cancer, adrenocortical carcinoma, pancreatic cancer, pancreatic adenocarcinoma, glioma, brain cancer, neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST), Waldenstrom's macroglobulinemia, or medulloblastoma.

[0117] In some embodiments, the cancer is hepatocellular carcinoma (HCC), hepatoblastoma, colon cancer, rectal cancer, ovarian cancer, ovarian epithelial cancer, ovarian carcinoma, fallopian tube cancer, papillary serous cystadenocarcinoma, uterine papillary serous carcinoma (UPSC), hepatocholangiocarcinoma, soft tissue and bone synovial sarcoma, rhabdomyosarcoma, osteosarcoma, anaplastic thyroid cancer, adrenocortical carcinoma, pancreatic cancer, pancreatic adenocarcinoma, glioma, neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST), Waldenstrom's macroglobulinemia, or medulloblastoma.

[0118] In some embodiments, the cancer is hepatocellular carcinoma (HCC). In some embodiments, the cancer is hepatoblastoma. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is rectal cancer. In some embodiments, the cancer is ovarian cancer, or ovarian carcinoma. In some embodiments, the cancer is ovarian epithelial cancer. In some embodiments, the cancer is fallopian tube cancer. In some embodiments, the cancer is papillary serous cystadenocarcinoma. In some embodiments, the cancer is uterine papillary serous carcinoma (UPSC). In some embodiments, the cancer is hepatocholangiocarcinoma. In some embodiments, the cancer is soft tissue and bone synovial sarcoma. In some embodiments, the cancer is rhabdomyosarcoma. In some embodiments, the cancer is osteosarcoma. In some embodiments, the cancer is anaplastic thyroid cancer. In some embodiments, the cancer is adrenocortical carcinoma. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is pancreatic adenocarcinoma. In some embodiments, the cancer is glioma. In some embodiments, the cancer is malignant peripheral nerve sheath tumors (MPNST). In some embodiments, the cancer is neurofibromatosis-1 associated MPNST. In

some embodiments, the cancer is Waldenstrom's macroglobulinemia. In some embodiments, the cancer is medulloblastoma.

[0119] In certain embodiments, the cancer is prostate cancer. In certain embodiments, the cancer is metastatic prostate cancer. In certain embodiments, the cancer is non-metastatic prostate cancer. In certain embodiments, the cancer is androgen indifferent prostate cancer (AIPC). In certain embodiments, the cancer is castration-resistant prostate cancer (CRPC). In certain embodiments, the cancer is a CRPC that is at high risk of progressing to CRPC-NE, or a CRPC that expresses elevated levels of NSD2 compared to non-cancerous prostate cells.

[0120] In certain embodiments, the cancer is metastatic castration-resistant prostate cancer (mCRPC). In certain embodiments, the cancer is non-metastatic castration-resistant prostate cancer (nmCRPC).

[0121] In certain embodiments, the cancer is castration-sensitive prostate cancer (CSPC). In certain embodiments, the cancer is metastatic castration-sensitive prostate cancer (mCSPC). In certain embodiments, the cancer is non-metastatic castration-sensitive prostate cancer (nmCSPC).

[0122] In certain embodiments, the cancer is hormone-sensitive prostate cancer (HSPC).

[0123] In certain embodiments, the cancer is small cell prostate carcinoma (SCPC). In certain embodiments, the cancer is large cell neuroendocrine carcinoma (LCNEC). In certain embodiments, the cancer is aggressive variant prostate cancer (AVPC). In certain embodiments, the cancer is hormone refractory prostate cancer. In certain embodiments, the cancer is neuroendocrine prostate cancer (NEPC). In certain embodiments, the cancer is small cell neuroendocrine prostate cancer or large cell neuroendocrine prostate cancer.

[0124] In certain embodiments, the cancer is glandular prostate cancer. In certain embodiments, the cancer is ductal prostate cancer, mucinous prostate cancer, or signet ring cell prostate cancer. In certain embodiments, the cancer is basal cell prostate cancer. In certain embodiments, the cancer is transitional cell prostate cancer. In certain embodiments, the cancer is a prostate sarcoma. In certain embodiments, the prostate cancer is a leiomyosarcoma or a rhabdomyosarcoma. In certain embodiments, the cancer is neuroendocrine castration-resistant prostate cancer (CRPC-NE). In certain embodiments, the cancer is a CRPC-NE lacking

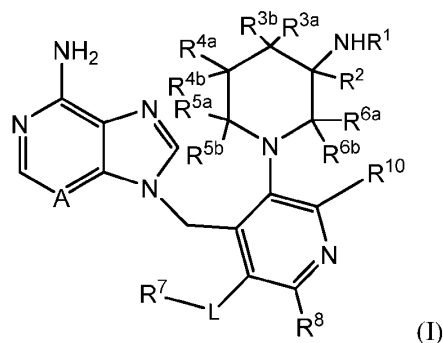
androgen receptor expression; a CRPC-NE lacking sensitivity to one or more androgen receptor pathway inhibitors, including but not limited to enzalutamide, abiraterone, apalutamide, bicalutamide, darolutamide, flutamide, nilutamide, and luteinizing hormone-releasing hormone (LHRH) agonists; or a CRPC-NE that expresses elevated levels of NSD2 compared to non-cancerous prostate cells.

[0125] In certain embodiments, the cancer is double-negative prostate cancer (DNPC). In certain embodiments, the cancer is androgen receptor (AR) pathway-independent prostate cancer. In certain embodiments, the cancer is mesenchymal and stem-like prostate cancer (MSPC). In certain embodiments, the cancer is enhancer-addicted prostate cancer. In certain embodiments, the cancer is high-risk localized prostate cancer. In certain embodiments, the cancer is advanced stage prostate cancer. In certain embodiments, the cancer is end-stage prostate cancer.

[0126] In certain embodiments, the cancer has an elevated level of expression of NSD2, such as a level of expression of NSD2 that is greater than that observed in normal healthy tissue.

First Therapeutic Agent

[0127] In certain embodiments, the first therapeutic agent is a compound of Formula (I):



or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof;
wherein:

A is N or CR⁹ wherein R⁹ is hydrogen or halo;

L is a bond or C₁₋₄ alkylene;

R¹ is H; or

R^1 and R^2 together with NH forms a 5-8 membered heterocyclyl containing 1-2 heteroatoms selected from N, O and S as ring members; wherein said 5-8 membered heterocyclyl is unsubstituted or substituted by an oxo substituent;

R^2 is selected from the group consisting of:

(i) hydrogen, $-C_{1-6}$ alkyl, $-haloC_{1-6}$ alkyl, $-hydroxyC_{1-6}$ alkylene, $-hydroxyhaloC_{1-6}$ alkylene, $-C_{1-6}alkoxyC_{1-6}alkylene$, $-haloC_{1-6}alkoxyC_{1-6}alkylene$ or $-C_{3-8}$ cycloalkoxy(C_{1-6} alkyl);

(ii) cyano; $-cyanoC_{1-6}$ alkylene; $-C_{1-6}$ alkylthio $C_{1-6}alkyl$; $-C_{2-6}$ alkenyl; $-haloC_{2-6}$ alkenyl; $-C_{2-6}$ alkynyl; $-C_{1-4}$ alkylSOC $C_{1-4}alkyl$; $-C_{1-4}$ alkylSO $C_{1-4}alkyl$; $-SO_2R^8$ or $-C(C_{1-4}alkyl)=N-O(C_{1-4}alkyl)$;

(iii) $-C_{1-4}alkylcarbonyl$; $-(CR^aR^b)_p-C(=O)-OR^{10}$; or $-C(=O)-(CR^aR^b)_qR^{11}$; wherein R^{11} is C_{3-7} cycloalkyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl, each of which is independently unsubstituted or substituted with C_{1-6} alkyl or C_{1-6} alkoxy;

(iv) $-(CR^aR^b)_r-C(=O)-NR^{12}R^{13}$ wherein R^{12} is hydrogen or C_{1-6} alkyl; R^{13} is hydrogen, $-C_{1-6}$ alkyl or a 5-6 membered heterocyclic ring; or R^{12} and R^{13} together form a 5-6 membered heterocyclic ring; wherein said 5-6 membered heterocyclic ring is unsubstituted or substituted with C_{1-4} alkyl;

(v) 5-6 membered heterocyclyl $C_{0-6}alkyl$ or 5-6 membered heterocyclyl($haloC_{1-4}alkyl$) wherein each said heterocyclyl radical is unsubstituted or substituted by oxo; and

(vi) 5-9 membered heteroaryl $C_{0-6}alkyl$ or 5-9 membered heteroaryl($haloC_{1-4}alkyl$), wherein each said heteroaryl radical is unsubstituted or substituted by $-C_{1-4}$ alkyl, $-haloC_{1-4}alkyl$, $-hydroxyC_{1-4}alkylene$, $-C_{1-4}alkoxy$, $-haloC_{1-4}alkoxy$, halo, hydroxy, cyano, oxido, $-aminocarbonylC_{0-6}alkyl$, $-C_{1-4}alkylaminocarbonylC_{0-6}alkyl$, $-diC_{1-4}alkylaminocarbonylC_{0-6}alkyl$ or $-C_{3-7}$ cycloalkyl;

R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{5a} , R^{5b} , R^{6a} and R^{6b} are independently hydrogen, halo, cyano, hydroxyl, $-C_{1-6}$ alkyl, $-haloC_{1-6}alkyl$, $-hydroxyC_{1-6}alkylene$, $-C_{1-6}alkoxy$, $-C_{1-6}alkoxyC_{1-6}alkylene$, $-haloC_{1-6}alkoxyC_{1-6}alkylene$, $-hydroxyhaloC_{1-6}alkylene$, aryl, $-C(=O)-OR^{14}$ or $-(CR^aR^b)_s-C(=O)-NR^{15}R^{16}$; or

R^{3a} and R^{3b} , R^{4a} and R^{4b} , R^{5a} and R^{5b} or R^{6a} and R^{6b} forms an oxo substituent;

R^7 is H, $-C_{1-4}alkoxy$, halo or $C_{1-4}alkyl$; or 3-8 membered heterocyclyl, which is unsubstituted or substituted by halo;

R^8 is C_{3-8} cycloalkyl(C_{0-6} alkyl); 4-6 membered heterocyclyl(C_{0-6} alkyl) comprising 1-3 heteroatoms selected from N, O and S; aryl or 5-9 membered heteroaryl(C_{0-6} alkyl) comprising 1-3 heteroatoms selected from N, O and S; wherein R^8 is unsubstituted or substituted by 1-3 R^{17} ;

R^{17} is halo, hydroxy, cyano, $-C_{1-6}$ alkyl, $-haloC_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-haloC_{1-6}$ alkoxy, $-NR^aC(=O)CR^c=C(R^c)_2$ or $-(CR^aR^b)_t-NR^a-C(=O)-R^{18}$;

R^a , R^b , R^c , R^{10} , R^{14} , R^{15} and R^{16} are independently hydrogen or $-C_{1-4}$ alkyl;

R^{18} is $-C_{1-4}$ alkyl or $-C_{1-4}$ haloalkyl; and

p, q, r, s and t are independently 0-4.

[0128] The definitions of variables in Formula I above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

[0129] In certain embodiments, the compound is a compound of Formula I.

[0130] In certain embodiments, A is N.

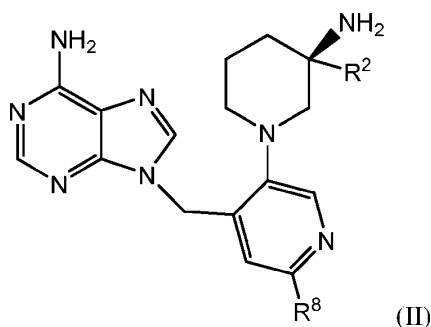
[0131] In certain embodiments, R^{3a} is hydrogen or halo; and R^{3b} is hydrogen, halo, $-hydroxyl$, $-C_{1-6}$ alkoxy or cyano; or R^{4a} is hydrogen or halo; and R^{4b} is hydrogen, halo, $-C_{1-6}alkoxyC_{1-6}alkylene$, $-C_{1-6}$ alkyl or $-haloC_{1-6}$ alkyl; or R^{5a} is hydrogen and R^{5b} is hydrogen or $-C_{1-6}$ alkyl; or R^{5a} and R^{5b} together form an oxo substituent.

[0132] In certain embodiments, R^{6a} is hydrogen or halo; R^{6b} is hydrogen, $-haloC_{1-6}alkoxyC_{1-6}alkylene$, $-hydroxyc_{1-6}alkylene$, $-hydroxyhaloC_{1-6}alkylene$, carboxyl, phenyl or $-(CR^aR^b)_t-C(O)-NR^{15}R^{16}$; R^a , R^b , R^{15} and R^{16} are independently hydrogen or $-C_{1-4}$ alkyl; and t is 0-1; or R^{6a} and R^{6b} together form an oxo substituent.

[0133] In certain embodiments, R^7 is H, $-C_{1-4}$ alkoxy or halo.

[0134] In certain embodiments, R^1 , R^{3a} , R^{3b} , R^{4a} , R^{4b} , R^{5a} , R^{5b} , R^{6a} , R^{6b} and R^7 are hydrogen.

[0135] In certain embodiments, said compound is a compound of Formula (II):

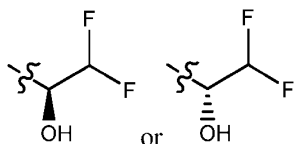


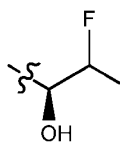
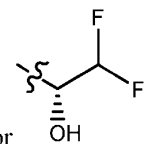
or an enantiomer, an enantiomeric mixture, or a pharmaceutically acceptable salt thereof.

[0136] In certain embodiments, R^2 is $-C_{1-6}$ alkyl, $-\text{halo}C_{1-6}$ alkyl, $-\text{hydroxy}C_{1-6}$ alkylene, $-\text{hydroxyhalo}C_{1-6}$ alkylene, $-C_{1-6}\text{alkoxy}C_{1-6}\text{alkylene}$, $-\text{halo}C_{1-6}\text{alkoxy}C_{1-6}\text{alkylene}$ or $-C_{3-8}$ cycloalkoxy(C_{1-6} alkyl).

[0137] In certain embodiments, R^2 is 2,2-difluoroethyl; 2-methyl-propan-1-olyl; ethan-1-olyl; 2,2-difluoroethan-1-olyl; 2-fluoroethan-1-olyl; 2,2,2-trifluoroethan-1-olyl; difluoromethoxyl; or 2,2,2-trifluoroethoxyl.

[0138] In certain embodiments, R^2 is 2,2-difluoroethyl; 2-methyl-propan-1-olyl; ethan-1-olyl; 2,2-difluoroethan-1-olyl; 2-fluoroethan-1-olyl; 2,2,2-trifluoroethan-1-olyl; difluoromethoxyl; or 2,2,2-trifluoroethoxyl.



[0139] In certain embodiments, R^2 is  or .

[0140] In certain embodiments, R^8 is phenyl substituted with 1-3 R^{17} ; wherein R^{17} is halo, hydroxy, cyano, $-C_{1-6}$ alkyl, $-\text{halo}C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-\text{halo}C_{1-6}$ alkoxy, $-\text{NR}^d\text{C}(\text{O})\text{CR}^d=\text{C}(\text{R}^d)_2$ or $-(\text{CR}^a\text{R}^b)_t-\text{NR}^d-\text{C}(\text{O})-\text{R}^{18}$; R^a , R^b and R^d are independently hydrogen or $-C_{1-4}$ alkyl; R^{18} is C_{1-4} haloalkyl; and t is 0-1.

[0141] In certain embodiments, R^8 is phenyl substituted with 1-3 R^{17} ;

R^{17} is halo, hydroxy, cyano, $-C_{1-6}$ alkyl, $-\text{halo}C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-\text{halo}C_{1-6}$ alkoxy, $-\text{NR}^d\text{C}(\text{O})\text{CR}^d=\text{C}(\text{R}^d)_2$ or $-(\text{CR}^a\text{R}^b)_t-\text{NR}^d-\text{C}(\text{O})-\text{R}^{18}$;

R^a , R^b and R^d are independently hydrogen or $-C_{1-4}$ alkyl;

R^{18} is C_{1-4} haloalkyl; and

t is 0-1.

[0142] In certain embodiments, R⁸ is phenyl substituted with 1-3 R¹⁷; and R¹⁷ is halo, hydroxy, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -C₁₋₆ alkoxy or -haloC₁₋₆ alkoxy.

[0143] In certain embodiments, R⁸ is phenyl substituted with 1-3 R¹⁷; and R¹⁷ is halo, hydroxy, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -C₁₋₆ alkoxy or -haloC₁₋₆ alkoxy.

[0144] In certain embodiments, said compound is selected from a compound in the following table, or a pharmaceutically acceptable salt thereof:

<u>No.</u>	<u>Chemical Name</u>
1	(R)-9-((5-(3-aminopiperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
2	9-((5-((3S,4R)-3-amino-4-fluoropiperidin-1-yl)-2-(2-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
3	(3S,4R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-4-ol
4	(R)-9-((5-(3-aminopiperidin-1-yl)-2-(3-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
5	9-((5-((3S,4R)-3-amino-4-fluoropiperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
6	(R)-9-((5-(3-aminopiperidin-1-yl)-2-(2-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
7	(R)-4-(4-((6-amino-9H-purin-9-yl)methyl)-5-(3-aminopiperidin-1-yl)pyridin-2-yl)-2-chlorobenzonitrile
8	9-((5-((3S,4R)-3-amino-4-fluoropiperidin-1-yl)-2-(3-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
9	4-(5-((2S,3R)-3-amino-2-(methoxymethyl)piperidin-1-yl)-4-((6-amino-9H-purin-9-yl)methyl)pyridin-2-yl)-2-fluorobenzonitrile
10	9-((5-((3S,4R)-3-amino-4-fluoropiperidin-1-yl)-2-(2-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
11	(R)-9-((5-(3-aminopiperidin-1-yl)-2-(4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
12	9-((5-((3S,4R)-3-amino-4-fluoropiperidin-1-yl)-2-(3-chlorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
13	4-(5-((3S,4R)-3-amino-4-fluoropiperidin-1-yl)-4-((6-amino-9H-purin-9-yl)methyl)pyridin-2-yl)-2-fluorobenzonitrile
14	9-((5-((3S,4R)-3-amino-4-fluoropiperidin-1-yl)-2-(2,3-dihydrobenzofuran-5-yl)pyridin-4-yl)methyl)-9H-purin-6-amine
15	9-((5-(3-amino-4-methoxypiperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine

<u>No.</u>	<u>Chemical Name</u>
16	(R)-9-((5-(5-amino-3,3-difluoropiperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
17	9-((5-(3-amino-4,4-difluoropiperidin-1-yl)-2-(3-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
18	3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidine-4-carbonitrile
19	(R)-1-((5-(3-aminopiperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-7-chloro-1H-imidazo[4,5-c]pyridin-4-amine
20	(R)-9-((5-(3-amino-3-methylpiperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
21	(R)-1-((5-(3-aminopiperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
22	(R)-9-((5-(3-amino-3-(cyclopropoxymethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
23	(R)-9-((5-(3-amino-3-(methoxymethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
24	(R)-9-((5-(3-amino-3-(methoxymethyl)piperidin-1-yl)-2-(3-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
25	(R)-9-((5-(3-amino-3-(isopropoxymethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
26	(R)-9-((5-(3-amino-3-(methoxymethyl)piperidin-1-yl)-2-(5-chloro-2-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
27	(R)-9-((5-(3-amino-3-(methoxymethyl)piperidin-1-yl)-2-(3-chlorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
28	(R)-9-((5-(3-amino-3-(methoxymethyl)piperidin-1-yl)-2-(3-chloro-4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
29	(R)-9-((5-(3-amino-3-(methoxymethyl)piperidin-1-yl)-2-(2,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
30	(R)-9-((5-(3-amino-3-(cyclobutoxymethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
31	(R)-9-((5-(3-amino-3-(cyclopropoxymethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
32	(R)-9-((5-(3-amino-3-(cyclobutoxymethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
33	(R)-9-((5-(3-amino-3-(methoxymethyl)piperidin-1-yl)-2-(2-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
34	(R)-9-((5-(3-amino-3-(isopropoxymethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine

<u>No.</u>	<u>Chemical Name</u>
35	(R)-9-((5-(3-amino-3-(cyclobutoxymethyl)piperidin-1-yl)-2-(3-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
36	(R)-9-((5-(3-amino-3-(cyclobutoxymethyl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
37	(R)-9-((5-(3-amino-3-(isopropoxymethyl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
38	(R)-9-((5-(3-amino-3-(methoxymethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
39	(R)-9-((5-(3-amino-3-((2,2,2-trifluoroethoxy)methyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
40	(R)-9-((5-(3-amino-3-((difluoromethoxy)methyl)piperidin-1-yl)-2-(3-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
41	(R)-9-((5-(3-amino-3-((difluoromethoxy)methyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
42	(R)-9-((5-(3-amino-3-((difluoromethoxy)methyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
43	(R)-9-((5-(3-amino-3-((2,2,2-trifluoroethoxy)methyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
44	(R)-9-((5-(3-amino-3-((difluoromethoxy)methyl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
45	(R)-9-((5-(3-amino-3-((2,2,2-trifluoroethoxy)methyl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
46	(R)-1-((5-(3-amino-3-(methoxymethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
47	(S)-9-((5-(3-amino-3-(2,2-difluoroethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
48	(S)-1-((5-(3-amino-3-(thiazol-2-ylmethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
49	(S)-1-((5-(3-amino-3-((1-methyl-1H-pyrazol-3-yl)methyl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
50	(S)-1-((5-(3-amino-3-(pyridin-2-ylmethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
51	(S)-1-((5-(3-amino-3-(pyridin-2-ylmethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
52	(S)-9-((5-(3-amino-3-(oxazol-2-ylmethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
53	(S)-9-((5-(3-amino-3-(thiazol-2-ylmethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine

<u>No.</u>	<u>Chemical Name</u>
54	(S)-9-((5-(3-amino-3-(pyridin-2-ylmethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
55	(S)-9-((5-(3-amino-3-((6-methylpyridin-2-yl)methyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
56	(S)-9-((5-(3-amino-3-((1-methyl-1H-pyrazol-3-yl)methyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
57	(S)-1-((5-(3-amino-3-(thiazol-2-ylmethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
58	(S)-2-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluorophenyl)pyridin-3-yl)piperidin-3-yl)acetic acid
59	(S)-2-(3-amino-1-(4-((4-amino-1H-imidazo[4,5-c]pyridin-1-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-N,N-dimethylacetamide
60	9-((5-(3-amino-3-(2-methoxyethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
61	(S)-9-((5-(3-amino-3-(2,2-difluoroethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
62	(S)-2-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)acetamide
63	(S)-1-((5-(3-amino-3-(oxazol-2-ylmethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
64	N-(4-(5-(3-amino-3-(2,2-difluoroethyl)piperidin-1-yl)-4-((6-amino-9H-purin-9-yl)methyl)pyridin-2-yl)phenyl)-3-bromopropanamide
65	9-((5-((S)-3-amino-3-((R)-1-(pyridin-2-yl)ethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
66	2-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-N-methylacetamide
67	2-(3-amino-1-(4-((4-amino-7-chloro-1H-imidazo[4,5-c]pyridin-1-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-N-methylacetamide
68	2-(3-amino-1-(4-((4-amino-7-chloro-1H-imidazo[4,5-c]pyridin-1-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-N,N-dimethylacetamide
69	9-((5-(3-amino-3-((6-fluoropyridin-2-yl)methyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
70	(S)-2-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-N,N-dimethylacetamide
71	(S)-9-((5-(3-amino-3-(2,2-difluoroethyl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
72	2-(3-amino-1-(4-((4-amino-1H-imidazo[4,5-c]pyridin-1-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-N-methylacetamide

<u>No.</u>	<u>Chemical Name</u>
73	methyl (S)-2-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluorophenyl)pyridin-3-yl)piperidin-3-yl)acetate
74	(S)-9-((5-(3-amino-3-(pyrazin-2-ylmethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
75	N-(4-(5-(3-amino-3-(2,2-difluoroethyl)piperidin-1-yl)-4-((6-amino-9H-purin-9-yl)methyl)pyridin-2-yl)benzyl)-2-chloroacetamide
76	N-(4-(5-(3-amino-3-(2,2-difluoroethyl)piperidin-1-yl)-4-((6-amino-9H-purin-9-yl)methyl)pyridin-2-yl)phenyl)acrylamide
77	2-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)acetonitrile
78	(R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluorophenyl)pyridin-3-yl)-N-methylpiperidine-3-carboxamide
79	methyl (R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluorophenyl)pyridin-3-yl)piperidine-3-carboxylate
80	(R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)-N,N-dimethylpiperidine-3-carboxamide
81	isopropyl (R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)piperidine-3-carboxylate
82	(R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)-N-(tetrahydro-2H-pyran-4-yl)piperidine-3-carboxamide
83	tert-butyl (R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)piperidine-3-carboxylate
84	(R)-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(pyrrolidin-1-yl)methanone
85	3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)piperidine-3-carboxamide
86	(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(piperidin-1-yl)methanone
87	(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(2-methylpiperidin-1-yl)methanone
88	(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(2-methylpyrrolidin-1-yl)methanone
89	1-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,3-dimethylbutan-1-one
90	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)ethan-1-ol
91	9-((5-((R)-3-amino-3-((S)-fluoro(pyridin-2-yl)methyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine

<u>No.</u>	<u>Chemical Name</u>
92	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)ethan-1-ol
93	9-((5-((R)-3-amino-3-((S)-1-methoxyethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
94	9-((5-((R)-3-amino-3-((R)-1-methoxyethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
95	9-((5-((R)-3-amino-3-((S)-1-methoxyethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
96	(E)-1-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)ethan-1-one O-methyl oxime
97	9-((5-((R)-3-amino-3-((R)-1-methoxyethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
98	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2-methylpropan-1-ol
99	9-((5-(3-amino-3-((R)-1-methoxyethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
100	(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(cyclopentyl)methanone
101	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2-methylbutan-1-one
102	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2-methylbutan-1-one
103	1-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2-cyclopropylpropan-1-one
104	(R)-1-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2-methylpropan-1-one
105	(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(cyclobutyl)methanone
106	(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(3-methoxycyclopentyl)methanone
107	(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(1-methylcyclopropyl)methanone
108	(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(tetrahydro-2H-pyran-4-yl)methanone
109	(R)-1-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-dimethylpropan-1-one
110	(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(1-methyl-1H-pyrazol-3-yl)methanone

<u>No.</u>	<u>Chemical Name</u>
111	(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(tetrahydrofuran-3-yl)methanone
112	(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)(3-methyloxetan-3-yl)methanone
113	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol; or
114	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
115	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethyl)-2-methylphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
116	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethoxy)-3-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
117	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4,5-difluoro-2-methylphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
118	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)-5-methoxypyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
119	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethoxy)-3-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
120	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethyl)-2,5-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
121	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-chloro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
122	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-chloro-4-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
123	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(6-fluoro-1-methyl-1H-indazol-5-yl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
124	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-chloro-3-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
125	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-chloro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
126	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,4-dimethylphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
127	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
128	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethoxy)-2,5-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

No.	Chemical Name
129	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethyl)-5-fluoro-2-methylphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
130	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-cyclohexylpyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
131	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-fluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
132	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethyl)-2-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
133	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-chloro-2-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
134	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethyl)-2,5-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
135	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-5-fluoro-6-(2-fluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
136	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(1,6-dimethyl-1H-indazol-5-yl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
137	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethyl)-2-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
138	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethoxy)-2-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
139	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-chloro-4-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
140	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethyl)-2-methylphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
141	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2-fluoro-4-(trifluoromethyl)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
142	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,4-difluorophenyl)-5-fluoropyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
143	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(6-fluoro-1-methyl-1H-indazol-5-yl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
144	4-(5-((R)-3-amino-3-((S)-2,2-difluoro-1-hydroxyethyl)piperidin-1-yl)-4-((6-amino-9H-purin-9-yl)methyl)pyridin-2-yl)-2,5-difluorophenol
145	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-cyclohexylpyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
146	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2-(difluoromethyl)-4,5-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
147	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

<u>No.</u>	<u>Chemical Name</u>
148	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-chloro-2-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
149	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)-5-fluoropyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
150	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethoxy)-2,5-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
151	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
152	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-chloro-3-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
153	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-(difluoromethoxy)-2-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
154	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3-(difluoromethyl)-2,5-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
155	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-5'-fluoro-[2,2'-bipyridin]-5-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
156	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,4,5-trifluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol; or (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,4,5-trifluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
157	
158	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2-(difluoromethyl)-4-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol; or (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2-(difluoromethyl)-4-fluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
159	
160	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol; or (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
161	
162	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2-(difluoromethyl)-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol; or (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2-(difluoromethyl)-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
163	
164	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol; or
165	

No.	Chemical Name
	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
166	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-methoxy-2-(trifluoromethyl)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol; or (R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-methoxy-2-(trifluoromethyl)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
167	
168	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2-chloro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol; or (R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2-chloro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
169	
170	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2-(difluoromethyl)-4,5-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol; or (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2-(difluoromethyl)-4,5-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
171	
172	(R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,3,4-trifluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
173	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-fluoro-2-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol; or (R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(4-fluoro-2-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
174	
175	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6'-chloro-5'-fluoro-[2,2'-bipyridin]-5-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol; or (R)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6'-chloro-5'-fluoro-[2,2'-bipyridin]-5-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol
176	
177	9-((5-(3-amino-3-(6-methylpyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
178	(R)-9-((5-(3-amino-3-(6-methoxypyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
179	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(1,3-dihydroisobenzofuran-5-yl)pyridin-4-yl)methyl)-9H-purin-6-amine
180	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-5'-chloro-6'-fluoro-[2,3'-bipyridin]-4-yl)methyl)-9H-purin-6-amine
181	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(2-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
182	(R)-9-((5-(3-amino-3-(6-cyclopropylpyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine

<u>No.</u>	<u>Chemical Name</u>
183	9-((5-((R)-3-amino-3-(6-((S)-1-fluoroethyl)pyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
184	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(4-(difluoromethoxy)phenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
185	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(2,3-dihydrobenzofuran-5-yl)pyridin-4-yl)methyl)-9H-purin-6-amine
186	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(benzo[d][1,3]dioxol-5-yl)pyridin-4-yl)methyl)-9H-purin-6-amine
187	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(2,5-difluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
188	(R)-9-((5-(3-amino-3-(6-chloro-5-fluoropyridin-2-yl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
189	9-((5-(3-amino-3-(5-fluoropyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
190	(R)-9-((5-(3-amino-3-(5-fluoro-6-methylpyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
191	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-6'-chloro-5'-fluoro-[2,2'-bipyridin]-4-yl)methyl)-9H-purin-6-amine
192	(R)-9-((5-(3-amino-3-(6-chloro-3-fluoropyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
193	9-((5-(3-amino-3-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
194	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-6'-chloro-5'-methoxy-[2,2'-bipyridin]-4-yl)methyl)-9H-purin-6-amine
195	6-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)picolinamide
196	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-5'-fluoro-[2,2'-bipyridin]-4-yl)methyl)-9H-purin-6-amine
197	(R)-9-((5-(3-amino-3-(6-(1,1-difluoroethyl)pyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
198	(R)-9-((5-(3-amino-3-(pyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
199	(R)-9-((5-(3-amino-3-(3-fluoropyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
200	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
201	(R)-9-((5-(3-amino-3-(6-fluoropyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine

<u>No.</u>	<u>Chemical Name</u>
202	(R)-9-((5-(3-amino-3-(6-ethylpyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
203	(R)-9-((5-(3-amino-3-(6-(difluoromethyl)pyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
204	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-cyclopropylpyridin-4-yl)methyl)-9H-purin-6-amine
205	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
206	(R)-2-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-6-fluoropyridin-4-ol
207	(R)-9-((5-(3-amino-3-(5-fluoro-6-methylpyridin-2-yl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
208	6-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)picolinonitrile
209	(R)-9-((5-(3-amino-3-(5-(difluoromethoxy)pyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
210	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(imidazo[1,2-a]pyridin-6-yl)pyridin-4-yl)methyl)-9H-purin-6-amine
211	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
212	9-((5-((R)-3-amino-3-(6-((R)-1-fluoroethyl)pyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
213	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
214	6-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2-fluoropyridin-3-ol
215	1-(6-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2-fluoropyridin-3-yl)ethan-1-ol
216	(R)-9-((5-(3-amino-3-(6-chloro-5-fluoropyridin-2-yl)piperidin-1-yl)-2-(4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
217	(R)-6-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)pyridin-2-ol
218	(R)-9-((5-(3-amino-3-(6-(difluoromethyl)-5-fluoropyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
219	(R)-2-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-6-chloropyridin-4-ol
220	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(1-methyl-1H-benzo[d]imidazol-6-yl)pyridin-4-yl)methyl)-9H-purin-6-amine

<u>No.</u>	<u>Chemical Name</u>
221	(R)-9-((5-(3-amino-3-(6-chloro-5-fluoropyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
222	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(pyrazolo[1,5-a]pyridin-6-yl)pyridin-4-yl)methyl)-9H-purin-6-amine
223	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(pyrazolo[1,5-a]pyridin-6-yl)pyridin-4-yl)methyl)-9H-purin-6-amine
224	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-6'-fluoro-5'-methoxy-[2,2'-bipyridin]-4-yl)methyl)-9H-purin-6-amine
225	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(1-methyl-1H-indazol-5-yl)pyridin-4-yl)methyl)-9H-purin-6-amine
226	(R)-9-((5-(3-amino-3-(6-(fluoromethyl)pyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
227	(R)-9-((5-(3-amino-3-(6-(difluoromethyl)pyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
228	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(4-(difluoromethoxy)-3-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
229	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-4-yl)methyl)-9H-purin-6-amine
230	(R)-9-((5-(3-amino-3-(6-chloro-3-methoxypyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
231	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-5'-fluoro-6'-methoxy-[2,3'-bipyridin]-4-yl)methyl)-9H-purin-6-amine
232	(R)-2-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-6-methylpyridine 1-oxide
233	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(3,5-difluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
234	1-(6-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2-chloropyridin-3-yl)ethan-1-ol
235	(R)-9-((5-(3-amino-3-(6-fluoro-4-methoxypyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
236	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(2,6-difluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
237	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(2,6-difluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
238	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(2,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
239	(R)-2-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-6-fluoropyridin-3-ol

<u>No.</u>	<u>Chemical Name</u>
240	9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-5',6'-difluoro-[2,3'-bipyridin]-4-yl)methyl)-9H-purin-6-amine
241	(R)-9-((5-(3-amino-3-(5-fluoro-6-methylpyridin-2-yl)piperidin-1-yl)-2-(4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
242	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(2,3-difluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
243	(R)-9-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-4'-fluoro-5'-methoxy-[2,2'-bipyridin]-4-yl)methyl)-9H-purin-6-amine
244	5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-4-((6-amino-9H-purin-9-yl)methyl)-5'-fluoro-[2,3'-bipyridin]-6'-ol
245	(S)-9-((5-(3-amino-3-(pyridin-4-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
246	(S)-9-((5-(3-amino-3-(2-chloropyridin-4-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
247	(S)-9-((5-(3-amino-3-(2-methylpyridin-4-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
248	(S)-9-((5-(3-amino-3-(3-fluoropyridin-4-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
249	9-((5-(3-amino-3-(6-chloropyridazin-3-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
250	(R)-9-((5-(3-amino-3-(6-ethylpyrazin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
251	(R)-9-((5-(3-amino-3-(2-ethylpyrimidin-4-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
252	(R)-1-((5-(3-amino-3-(6-ethylpyridin-2-yl)piperidin-1-yl)-2-cyclopropylpyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
253	9-((5-(3-amino-3-(pyridazin-3-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
254	9-((5-(3-amino-3-(6-chloropyrazin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
255	9-((5-(3-amino-3-(pyrimidin-4-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
256	(R)-1-((5-(3-amino-3-(6-ethylpyrazin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
257	(R)-9-((5-(3-amino-3-(2-methylpyrimidin-4-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
258	(R)-9-((5-(3-amino-3-(6-methylpyrazin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine

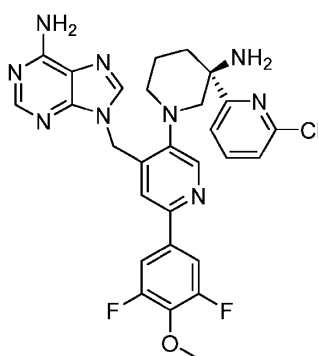
No.	Chemical Name
259	9-((5-(3-amino-3-(pyrazin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
260	(R)-1-((5-(3-amino-3-(6-(difluoromethyl)pyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
261	(R)-1-((5-(3-amino-3-(6-methylpyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
262	1-((5-(3-amino-3-(6-fluoropyridin-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
263	1-((5-(3-amino-3-(6-methylpyridin-2-yl)piperidin-1-yl)-2-cyclopropylpyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
264	(R)-1-((5-(3-amino-3-(6-(difluoromethyl)pyridin-2-yl)piperidin-1-yl)-2-cyclopropylpyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
265	1-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-(azetidin-1-yl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
266	1-((5-(3-amino-3-(pyridin-2-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
267	1-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-cyclobutylpyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
268	1-((5-(3-amino-3-(6-chloropyridin-2-yl)piperidin-1-yl)-2-cyclobutylpyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
269	(S)-9-((5-(3-amino-3-(1-methyl-1H-pyrazol-4-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
270	1-((5-(3-amino-3-(1-methyl-1H-pyrazol-4-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
271	9-((5-(3-amino-3-(pyridin-3-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
272	(S)-3-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)pyridin-2(1H)-one
273	(R)-9-((5-(3-amino-3-(1-(difluoromethyl)-1H-pyrazol-3-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
274	(R)-9-((5-(3-amino-3-(1-isopropyl-1H-pyrazol-3-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
275	(R)-9-((5-(3-amino-3-(1-methyl-1H-pyrazol-3-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
276	(R)-1-((5-(3-amino-3-(1-ethyl-1H-pyrazol-3-yl)piperidin-1-yl)-2-cyclopropylpyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
277	1-((5-(3-amino-3-(1-ethyl-1H-pyrazol-3-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine

<u>No.</u>	<u>Chemical Name</u>
278	9-((5-(3-amino-3-(1-cyclopropyl-1H-pyrazol-3-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
279	(R)-1-((5-(3-amino-3-(1-(difluoromethyl)-1H-pyrazol-3-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
280	1-((5-(3-amino-3-(1-cyclopropyl-1H-pyrazol-3-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-1H-imidazo[4,5-c]pyridin-4-amine
281	9-((5-(3-amino-3-(2-chlorothiazol-4-yl)piperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
282	9-((5-(3-amino-3-(1-methyl-1H-1,2,3-triazol-4-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
283	(R)-9-((5-(3-amino-3-(2-methyl-2H-1,2,3-triazol-4-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
284	(R)-9-((5-(3-amino-3-(5-methylisoxazol-3-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
285	(R)-2-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2-fluoroethan-1-ol
286	(R)-2-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,4,5-trifluorophenyl)pyridin-3-yl)piperidin-3-yl)-2-fluoroethan-1-ol
287	9-((5-(3-amino-3-(1,2-difluoroethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
288	9-((5-((R)-3-amino-3-((2R,6S)-6-methyl-1,4-dioxan-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
289	9-((5-((R)-3-amino-3-((R)-1,4-dioxan-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
290	9-((5-((R)-3-amino-3-((R)-1,4-dioxan-2-yl)piperidin-1-yl)-2-(2,4,5-trifluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
291	9-((5-((R)-3-amino-3-((R)-1,4-dioxan-2-yl)piperidin-1-yl)-2-(2-(difluoromethyl)-4,5-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
292	(R)-7-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)-3-oxa-1,7-diazaspiro[4.5]decan-2-one
293	(S)-9-((5-(3-amino-3-(1,1-difluoroprop-1-en-2-yl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
294	9-((5-(3-amino-3-(2,2-difluorovinyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
295	9-((5-(3-amino-3-(1-fluoroethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
296	(R)-9-((5-(3-((1H-pyrazol-1-yl)methyl)-3-aminopiperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine

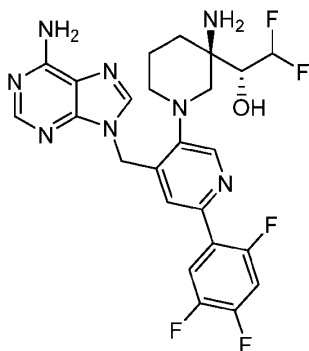
No.	Chemical Name
297	9-((5-(3-amino-3-((methylthio)methyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
298	9-((5-(3-amino-3-((methylsulfonyl)methyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
299	(S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-2,2,2-trifluoroethan-1-ol
300	9-((5-(3-amino-3-(1,2,2-trifluoroethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
301	3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)-3-(2,2-difluoroethyl)piperidin-4-ol
302	(3R,4R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)-3-(6-chloropyridin-2-yl)piperidin-4-ol
303	(S)-9-((5-(3-amino-3-(2,2,2-trifluoroethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
304	(S)-9-((5-(3-amino-3-ethynylpiperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
305	(R)-9-((5-(3-amino-3-(difluoromethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
306	9-((5-((3R,5R)-3-amino-5-(fluoromethyl)piperidin-1-yl)-2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
307	9-((5-((3S,5S)-3-amino-3-(2,2-difluoroethyl)-5-methylpiperidin-1-yl)-2-(4-fluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
308	9-((5-(3-amino-5-(methoxymethyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
309	9-((5-((3R,5S)-3-amino-5-fluoropiperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
310	9-((5-((2S,5R)-5-amino-2-methylpiperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
311	9-((5-((2S,3R)-3-amino-2-((difluoromethoxy)methyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
312	((2S,3R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-2-yl)methanol
313	9-((5-((2S,3R)-3-amino-2-((2,2-difluoroethoxy)methyl)piperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
314	2-((2R,3R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-2-yl)ethan-1-ol
315	(2S,3R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)-N-methylpiperidine-2-carboxamide

No.	Chemical Name
316	(R)-1-((2S,3R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-2-yl)-2,2,2-trifluoroethan-1-ol
317	(2S,3R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)-N,N-dimethylpiperidine-2-carboxamide
318	(2S,3R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidine-2-carboxamide
319	(2S,3R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidine-2-carboxamide
320	2-((2R,3R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-2-yl)acetamide
321	9-((2-(3,4-difluorophenyl)-5-(4-oxa-1,8-diazaspiro[5.5]undecan-8-yl)pyridin-4-yl)methyl)-9H-purin-6-amine
322	(S)-3-(3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-3-yl)-N,N-dimethylpropanamide
323	9-((5-((2R,3R)-3-amino-2-phenylpiperidin-1-yl)-2-(3,4-difluorophenyl)pyridin-4-yl)methyl)-9H-purin-6-amine
324	3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-2-one
325	(R)-5-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(3,4-difluorophenyl)pyridin-3-yl)piperidin-2-one

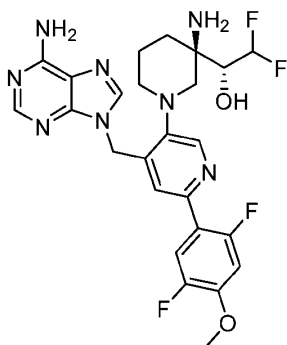
[0145] In certain embodiments, the first therapeutic agent has the following formula or a pharmaceutically acceptable salt thereof:



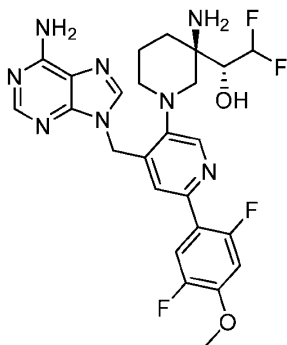
[0146] In certain embodiments, the first therapeutic agent has the following formula or a pharmaceutically acceptable salt thereof:



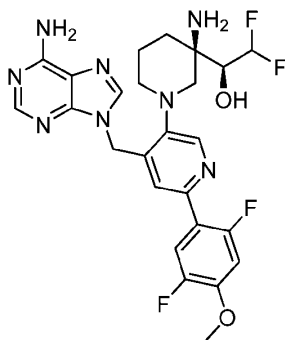
[0147] In certain embodiments, the first therapeutic agent has the following formula or a pharmaceutically acceptable salt thereof:



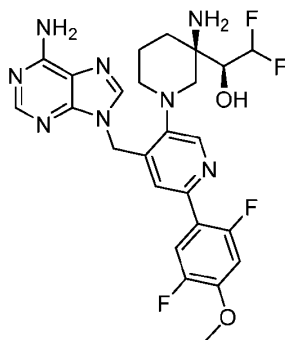
[0148] In certain embodiments, the first therapeutic agent has the formula:



[0149] In certain embodiments, the first therapeutic agent the following formula or a pharmaceutically acceptable salt thereof:



[0150] In certain embodiments, the first therapeutic agent has the formula:



Second Therapeutic Agent

[0151] In certain embodiments, the second therapeutic agent is (i) daratumumab, isatuximab, idecabtegene viciuecel, ciltacabtegene autoleucel, or belantamab mafodotin-blmf, (ii) bortezomib, carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, mezigdomide, iberdomide, selinexor, binemetinib, cobimetinib, selumetinib, refametinib, PD-0325901, or ROS126766, or a pharmaceutically acceptable salt thereof, (iii) dacomitinib, mobercitinib, neratinib, osimertinib, or vandetenib, or a pharmaceutically acceptable salt thereof, (iv) a bispecific antibody that binds CD3, (v) a tagged antibody, (vi) a chimeric antigen receptor (CAR) T-cell therapy cell therapy or a natural killer (NK) cell therapy, (vii) a natural killer cell engager, (viii) a KRAS inhibitor, (ix) an immune checkpoint inhibitor, (x) an FGFR3 inhibitor, (xi) an androgen receptor inhibitor, (xii) a BCL-2, BCLXL, or MCL1 inhibitor, (xiii) PARP inhibitor, (xiv) an androgen receptor degrader, or (xv) a radioligand therapy agent.

[0152] In certain embodiments, the second therapeutic agent is (i) daratumumab, isatuximab, idecabtegene vicleucel, ciltacabtegene autoleucel, or belantamab mafodotin-blmf, (ii) bortezomib, carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, mezigdomide, iberdomide, selinexor, binimetinib, cobimetinib, selumetinib, refametinib, PD-0325901, or ROS126766, or a pharmaceutically acceptable salt thereof, (iii) dacomitinib, mobercitinib, neratinib, osimertinib, or vandetenib, or a pharmaceutically acceptable salt thereof, (iv) a bispecific antibody that binds CD3, (v) a tagged antibody, (vi) a chimeric antigen receptor (CAR) T-cell therapy cell therapy or a natural killer (NK) cell therapy, (vii) a natural killer cell engager, (viii) a KRAS inhibitor, (ix) an immune checkpoint inhibitor, (x) an FGFR3 inhibitor, (xi) an androgen receptor inhibitor, (xii) a BCL-2, BCLXL, or MCL1 inhibitor, or a pharmaceutically acceptable salt thereof, (xiii) an androgen receptor degrader, or (xiv) a radioligand therapy agent.

[0153] In certain embodiments, the second therapeutic agent is (i) daratumumab, isatuximab, idecabtegene vicleucel, ciltacabtegene autoleucel, or belantamab mafodotin-blmf, (ii) bortezomib, carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, mezigdomide, iberdomide, selinexor, binimetinib, cobimetinib, selumetinib, refametinib, PD-0325901, or ROS126766, or a pharmaceutically acceptable salt thereof, (iii) dacomitinib, mobercitinib, neratinib, osimertinib, or vandetenib, or a pharmaceutically acceptable salt thereof, (iv) a bispecific antibody that binds CD3, (v) a tagged antibody, (vi) a chimeric antigen receptor (CAR) T-cell therapy cell therapy or a natural killer (NK) cell therapy, (vii) a natural killer cell engager, (viii) a KRAS inhibitor, (ix) an immune checkpoint inhibitor, (x) an FGFR3 inhibitor, (xi) an androgen receptor inhibitor, or (xii) a BCL-2, BCLXL, or MCL1 inhibitor.

[0154] In certain embodiments, the second therapeutic agent is (i) daratumumab, isatuximab, idecabtegene vicleucel, ciltacabtegene autoleucel, or belantamab mafodotin-blmf, (ii) carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, mezigdomide, iberdomide, selinexor, binimetinib, cobimetinib, selumetinib, refametinib, PD-0325901, or ROS126766, or a pharmaceutically acceptable salt thereof, (iii) dacomitinib, mobercitinib, neratinib, osimertinib, or vandetenib, or a pharmaceutically acceptable salt thereof, (iv) a bispecific antibody that binds CD3, (v) a tagged antibody, (vi) a chimeric antigen receptor (CAR) T-cell therapy cell therapy or a natural killer (NK) cell therapy, (vii) a natural killer cell engager, (viii) a KRAS inhibitor, (ix)

an immune checkpoint inhibitor, (x) an FGFR3 inhibitor, (xi) an androgen receptor inhibitor, or (xii) a BCL-2, BCLXL, or MCL1 inhibitor.

[0155] In certain embodiments, the second therapeutic agent is daratumumab, isatuximab, idecabtegene viciuecel, ciltacabtegene autoleucel, or belantamab mafodotin-blmf. In certain embodiments, the second therapeutic agent is daratumumab. In certain embodiments, the second therapeutic agent is isatuximab. In certain embodiments, the second therapeutic agent is idecabtegene viciuecel. In certain embodiments, the second therapeutic agent is ciltacabtegene autoleucel. In certain embodiments, the second therapeutic agent is belantamab mafodotin-blmf.

[0156] In certain embodiments, the second therapeutic agent is bortezomib, carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, mezigdomide, iberdomide, selinexor, binemetinib, cobimetinib, selumetinib, refametinib, PD-0325901, or ROS126766, or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, selinexor, binemetinib, cobimetinib, selumetinib, or refametinib, or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is binemetinib, cobimetinib, or selumetinib, or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is the second therapeutic agent is carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, mezigdomide, iberdomide, selinexor, binemetinib, cobimetinib, selumetinib, refametinib, PD-0325901, or ROS126766, or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent comprises (i) iberdomide or a pharmaceutically acceptable salt thereof and (ii) daratumumab.

[0157] In certain embodiments, the second therapeutic agent is bortezomib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is carfilzomib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is ixazomib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is thalidomide or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is lenalidomide or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is pomalidomide or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is mezigdomide or a pharmaceutically acceptable salt thereof. In

certain embodiments, the second therapeutic agent is iberdomide or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is selinexor or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is binimetinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is cobimetinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is selumetinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is cobimetinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is refametinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is PD-0325901 or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is ROS126766 or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is carfilzomib. In certain embodiments, the second therapeutic agent is pomalidomide. In certain embodiments, the second therapeutic agent is mezigdomide.

[0158] In certain embodiments, the second therapeutic agent is dacomitinib, mobercitinib, neratinib, osimertinib, or vandetenib, or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is dacomitinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is mobercitinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is neratinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is osimertinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is vandetenib or a pharmaceutically acceptable salt thereof.

[0159] In certain embodiments, the second therapeutic agent is a bispecific antibody that binds CD3.

[0160] In certain embodiments, the second therapeutic agent is (i) a bispecific antibody that binds CD3 and BCMA, (ii) a bispecific antibody that binds CD3 and GPRC5D, or (iii) a bispecific antibody that binds CD3 and FcRH5. In certain embodiments, the second therapeutic agent is a bispecific antibody that binds CD3 and BCMA. In certain embodiments, the second

therapeutic agent is a bispecific antibody that binds CD3 and GPRC5D. In certain embodiments, the second therapeutic agent is a bispecific antibody that binds CD3 and FcRH5.

[0161] In certain embodiments, the second therapeutic agent is teclistamab, elrantamab, alnuctamab, lomvoseltamab, ABV-383, HPN-217, talquetamab, forimtamig, cevostamab, or BMS-986393. In certain embodiments, the second therapeutic agent is teclistamab. In certain embodiments, the second therapeutic agent is elrantamab. In certain embodiments, the second therapeutic agent is alnuctamab. In certain embodiments, the second therapeutic agent is lomvoseltamab. In certain embodiments, the second therapeutic agent is ABV-383. In certain embodiments, the second therapeutic agent is HPN-217. In certain embodiments, the second therapeutic agent is talquetamab. In certain embodiments, the second therapeutic agent is forimtamig. In certain embodiments, the second therapeutic agent is cevostamab. In certain embodiments, the second therapeutic agent is BMS-986393.

[0162] In certain embodiments, the second therapeutic agent is a tagged antibody.

[0163] In certain embodiments, the tagged antibody is TAK-573.

[0164] In certain embodiments, the second therapeutic agent is a chimeric antigen receptor (CAR) T-cell therapy cell therapy or a natural killer (NK) cell therapy. In certain embodiments, the second therapeutic agent is a chimeric antigen receptor (CAR) T-cell therapy cell therapy. In certain embodiments, the second therapeutic agent is a natural killer (NK) cell therapy.

[0165] As used herein, the term “chimeric antigen receptor (CAR) T-cell therapy cell therapy,” “CAR-T therapy,” or “CAR-T therapy cell therapy” encompasses both autologous and allogenic CAR T-cell therapy cell therapy. In certain embodiments, the second therapeutic agent is a chimeric antigen receptor (CAR) T-cell therapy cell therapy, wherein the CAR T-cell therapy is an autologous CAR T-cell therapy cell therapy. In certain embodiments, the second therapeutic agent is a chimeric antigen receptor (CAR) T-cell therapy, wherein the CAR T-cell therapy is an allogenic CAR T-cell therapy cell therapy.

[0166] In certain embodiments, the second therapeutic agent is a chimeric antigen receptor (CAR) T-cell therapy cell therapy selected from idecabtagene vicleucel, ciltacabtagene autoleucel, CART-ddBCMA, CT-053, GC012F, MCAH109, or BMS-986393. In certain embodiments, the second therapeutic agent is idecabtagene vicleucel. In certain embodiments,

the second therapeutic agent is ciltacabtagene autoleucell. In certain embodiments, the second therapeutic agent is CART-ddBCMA. In certain embodiments, the second therapeutic agent is CT-053. In certain embodiments, the second therapeutic agent is GC012F. In certain embodiments, the second therapeutic agent is MCARH109. In certain embodiments, the second therapeutic agent is BMS-986393.

[0167] In certain embodiments, the second therapeutic agent is P-BCMA-ALLO1, ALLO-7715, FT538, FT576, or FT555T. In certain embodiments, the second therapeutic agent is P-BCMA-ALLO1. In certain embodiments, the second therapeutic agent is ALLO-7715. In certain embodiments, the second therapeutic agent is FT538. In certain embodiments, the second therapeutic agent is FT576. In certain embodiments, the second therapeutic agent is FT555T.

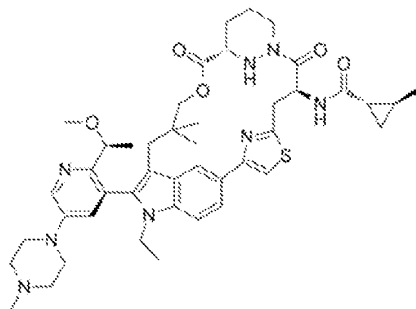
[0168] In certain embodiments, the second therapeutic agent is a natural killer cell engager.

[0169] In certain embodiments, the second therapeutic agent is a natural killer cell engager selected from CYT-338 or CC-92328. In certain embodiments, the second therapeutic agent is CYT-338. In certain embodiments, the second therapeutic agent is CC-92328.

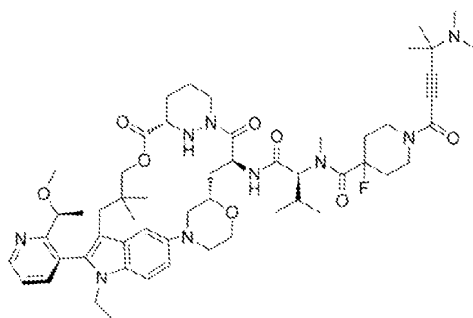
[0170] In certain embodiments, the second therapeutic agent is a KRAS inhibitor.

[0171] In certain embodiments, the second therapeutic agent is a KRAS inhibitor selected from sotorasib, adagrasib, JNJ-74699157, LY3499446, LY3537982, GDC-6036, D-1553, JDQ-443, BI 1823911, or AZD4625, or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is sotorasib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is adagrasib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is JNJ-74699157 or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is LY3499446 or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is LY3537982 or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is GDC-6036 or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is D-1553 or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is JDQ-443 or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is BI 1823911 or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is AZD4625 or a pharmaceutically acceptable salt thereof. In certain

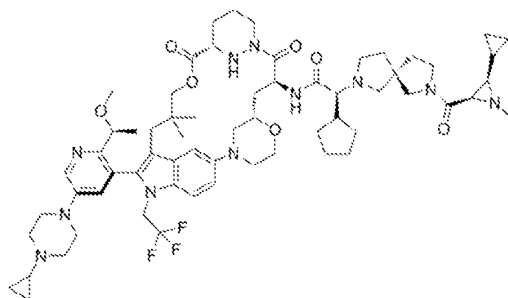
embodiments, the second therapeutic agent is MRTX1133. In certain embodiments, the second therapeutic agent is compound RMC-6236, RMC-6291, RMC-9805, or a pharmaceutically acceptable salt thereof. Compound RMC-6236 has the following chemical structure:



[0172] Compound RMC-6291 has the following chemical structure:



[0173] Compound RMC-9805 has the following chemical structure:



[0174] In certain embodiments, the second therapeutic agent is a pan-RAS inhibitor.

[0175] In certain embodiments, the second therapeutic agent is BI3706674, MRTX1133, RMC-6236, RMC-6291, RMC-9805, or ASP3082, or a pharmaceutically acceptable salt thereof.

[0176] In certain embodiments, the second therapeutic agent is an immune checkpoint inhibitor.

[0177] In certain embodiments, the second therapeutic agent is an immune checkpoint inhibitor selected from nivolumab and pembrolizumab. In certain embodiments, the second therapeutic agent is nivolumab. In certain embodiments, the second therapeutic agent is pembrolizumab.

[0178] In certain embodiments, the second therapeutic agent is an FGFR3 inhibitor.

[0179] In certain embodiments, the second therapeutic agent is an FGFR3 inhibitor selected from dovitinib, erdafitinib, INCB054828, JNJ-42756493, rogaratinib, or TYRA-300, or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is dovitinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is erdafitinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is INCB054828 or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is JNJ-42756493 or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is rogaratinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is TYRA-300 or a pharmaceutically acceptable salt thereof.

[0180] In certain embodiments, the second therapeutic agent is an FGFR3 inhibitor that is an anti-FGFR3 antibody selected from PRO-001, B-701, or R3Mab. In certain embodiments, the second therapeutic agent is PRO-001. In certain embodiments, the second therapeutic agent is B-701. In certain embodiments, the second therapeutic agent is R3Mab.

[0181] In certain embodiments, the second therapeutic agent is an androgen receptor inhibitor. In certain embodiments, the second therapeutic agent is an androgen receptor pathway inhibitor.

[0182] In certain embodiments, the second therapeutic agent is an androgen receptor inhibitor selected from apalutamide, enzalutamide, darolutamide, abiraterone, flutamide, and bicalutamide, or a pharmaceutically acceptable salt thereof. In certain embodiments, the second

therapeutic agent is apalutamide or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is enzalutamide or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is darolutamide or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is abiraterone or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is flutamide or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is bicalutamide or a pharmaceutically acceptable salt thereof.

[0183] In certain embodiments, a method of treating cancer provided herein further comprises administering to the subject a BCL-2, BCLXL, or MCL1 inhibitor, or a pharmaceutically acceptable salt thereof. In certain embodiments, a method of treating cancer provided herein further comprises administering to the subject a BCL-2 inhibitor, or a pharmaceutically acceptable salt thereof. In certain embodiments, a method of treating cancer provided herein further comprises administering to the subject a BCLXL inhibitor, or a pharmaceutically acceptable salt thereof. In certain embodiments, a method of treating cancer provided herein further comprises administering to the subject a MCL1 inhibitor, or a pharmaceutically acceptable salt thereof.

[0184] In certain embodiments, the BCL-2, BCLXL, or MCL1 inhibitor is selected from venetoclax, navitoclax, ABT-737, A-1155463, A-1331852, A64315, AMG397, AMG176, AZD5991, and ABBV467, or a pharmaceutically acceptable salt thereof.

[0185] In certain embodiments, the BCL-2, BCLXL, or MCL1 inhibitor is Venetoclax or a pharmaceutically acceptable salt thereof. In certain embodiments, the BCL-2, BCLXL, or MCL1 inhibitor is navitoclax or a pharmaceutically acceptable salt thereof. In certain embodiments, the BCL-2, BCLXL, or MCL1 inhibitor is ABT-737 or a pharmaceutically acceptable salt thereof. In certain embodiments, the BCL-2, BCLXL, or MCL1 inhibitor is A-1155463 or a pharmaceutically acceptable salt thereof. In certain embodiments, the BCL-2, BCLXL, or MCL1 inhibitor is A-1331852 or a pharmaceutically acceptable salt thereof. In certain embodiments, the BCL-2, BCLXL, or MCL1 inhibitor is A64315 or a pharmaceutically acceptable salt thereof. In certain embodiments, the BCL-2, BCLXL, or MCL1 inhibitor is AMG397 or a pharmaceutically acceptable salt thereof. In certain embodiments, the BCL-2,

BCLXL, or MCL1 inhibitor is AMG176 or a pharmaceutically acceptable salt thereof. In certain embodiments, the BCL-2, BCLXL, or MCL1 inhibitor is AZD5991 or a pharmaceutically acceptable salt thereof. In certain embodiments, the BCL-2, BCLXL, or MCL1 inhibitor is ABBV467 or a pharmaceutically acceptable salt thereof.

[0186] In certain embodiments, a method of treating cancer provided herein further comprises administering to the subject a tyrosine kinase inhibitor.

[0187] In certain embodiments, the method further comprises administering to the subject a tyrosine kinase inhibitor selected from cabozantinib, axitinib, lenvatinib, pazopanib, regorafenib, and sorafenib, or a pharmaceutically acceptable salt thereof. In certain embodiments, the method further comprises administering to the subject cabozantinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the method further comprises administering to the subject axitinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the method further comprises administering to the subject lenvatinib or a pharmaceutically acceptable salt thereof. In certain embodiments, the method further comprises administering to the subject pazopanib or a pharmaceutically acceptable salt thereof. In certain embodiments, the method further comprises administering to the subject regorafenib or a pharmaceutically acceptable salt thereof. In certain embodiments, the method further comprises administering to the subject sorafenib or a pharmaceutically acceptable salt thereof.

[0188] In certain embodiments, a method of treating cancer provided herein further comprises administering to the subject a PD-1 inhibitor.

[0189] In certain embodiments, the method further comprises administering to the subject a PD-1 inhibitor selected from pembrolizumab, nivolumab, and cemiplimab. In certain embodiments, the method further comprises administering to the subject pembrolizumab. In certain embodiments, the method further comprises administering to the subject nivolumab. In certain embodiments, the method further comprises administering to the subject cemiplimab.

[0190] In certain embodiments, a method of treating cancer provided herein further comprises administering to the subject a PD-L1 inhibitor.

[0191] In certain embodiments, the method further comprises administering to the subject a PD-L1 inhibitor selected from atezolizumab, avelumab, and durvalumab. In certain

embodiments, the method further comprises administering to the subject atezolizumab. In certain embodiments, the method further comprises administering to the subject avelumab. In certain embodiments, the method further comprises administering to the subject durvalumab.

[0192] In certain embodiments, the second therapeutic agent is an ALK Inhibitor, an ATR Inhibitor, an A2A Antagonist, a Base Excision Repair Inhibitor, a Bcr-Abl Tyrosine Kinase Inhibitor, a Bruton's Tyrosine Kinase Inhibitor, a CDC7 Inhibitor, a CHK1 Inhibitor, a Cyclin-Dependent Kinase Inhibitor, a DNA-PK Inhibitor, an Inhibitor of both DNA-PK and mTOR, a DNMT1 Inhibitor, a DNMT1 Inhibitor plus 2-chloro-deoxyadenosine, an HDAC Inhibitor, a Hedgehog Signaling Pathway Inhibitor, an IDO Inhibitor, a JAK Inhibitor, a mTOR Inhibitor, a MEK Inhibitor, a MELK Inhibitor, a MTH1 Inhibitor, a PARP Inhibitor, a Phosphoinositide 3-Kinase Inhibitor, an Inhibitor of both PARP1 and DHODH, a Proteasome Inhibitor, a Topoisomerase-II Inhibitor, a Tyrosine Kinase Inhibitor, a VEGFR Inhibitor, or a WEE1 Inhibitor.

[0193] In certain embodiments, the second therapeutic agent is an ALK Inhibitor. In certain embodiments, the second therapeutic agent is an ALK Inhibitor comprising ceritinib or crizotinib. In certain embodiments, the second therapeutic agent is an ATR Inhibitor. In certain embodiments, the second therapeutic agent is an ATR Inhibitor comprising AZD6738 or VX-970. In certain embodiments, the second therapeutic agent is an A2A Antagonist. In certain embodiments, the second therapeutic agent is a Base Excision Repair Inhibitor comprising methoxyamine. In certain embodiments, the second therapeutic agent is a Base Excision Repair Inhibitor, such as methoxyamine. In certain embodiments, the second therapeutic agent is a Bcr-Abl Tyrosine Kinase Inhibitor. In certain embodiments, the second therapeutic agent is a Bcr-Abl Tyrosine Kinase Inhibitor comprising dasatinib or nilotinib. In certain embodiments, the second therapeutic agent is a Bruton's Tyrosine Kinase Inhibitor. In certain embodiments, the second therapeutic agent is a Bruton's Tyrosine Kinase Inhibitor comprising ibrutinib. In certain embodiments, the second therapeutic agent is a CDC7 Inhibitor. In certain embodiments, the second therapeutic agent is a CDC7 Inhibitor comprising RXDX-103 or AS-141.

[0194] In certain embodiments, the second therapeutic agent is a CHK1 Inhibitor. In certain embodiments, the second therapeutic agent is a CHK1 Inhibitor comprising MK-8776, ARRY-575, or SAR-020106. In certain embodiments, the second therapeutic agent is a Cyclin-

Dependent Kinase Inhibitor. In certain embodiments, the second therapeutic agent is a Cyclin-Dependent Kinase Inhibitor comprising selinexor. In certain embodiments, the second therapeutic agent is a DNA-PK Inhibitor. In certain embodiments, the second therapeutic agent is a DNA-PK Inhibitor comprising MSC2490484A. In certain embodiments, the second therapeutic agent is Inhibitor of both DNA-PK and mTOR. In certain embodiments, the second therapeutic agent comprises CC-115.

[0195] In certain embodiments, the second therapeutic agent is a DNMT1 Inhibitor. In certain embodiments, the second therapeutic agent is a DNMT1 Inhibitor comprising decitabine, RX-3117, guadecitabine, NUC-8000, or azacytidine. In certain embodiments, the second therapeutic agent comprises a DNMT1 Inhibitor and 2-chloro-deoxyadenosine. In certain embodiments, the second therapeutic agent comprises ASTX-727.

[0196] In certain embodiments, the second therapeutic agent is a HDAC Inhibitor. In certain embodiments, the second therapeutic agent is a HDAC Inhibitor comprising OBP-801, CHR-3996, etinostat, resminostat, pracinostat, CG-200745, selinexor, romidepsin, mocetinostat, belinostat, AR-42, ricolinostat, KA-3000, or ACY-241.

[0197] In certain embodiments, the second therapeutic agent is a Hedgehog Signaling Pathway Inhibitor. In certain embodiments, the second therapeutic agent is a Hedgehog Signaling Pathway Inhibitor comprising sonidegib or vismodegib. In certain embodiments, the second therapeutic agent is an IDO Inhibitor. In certain embodiments, the second therapeutic agent is an IDO Inhibitor comprising INCB024360. In certain embodiments, the second therapeutic agent is an IDO Inhibitor selected from navoximod, indoximod, BMS-986205, PF-06840003, and BGS-5777. In certain embodiments, the second therapeutic agent is a JAK Inhibitor. In certain embodiments, the second therapeutic agent is a JAK Inhibitor comprising ruxolitinib or tofacitinib. In certain embodiments, the second therapeutic agent is a mTOR Inhibitor. In certain embodiments, the second therapeutic agent is a mTOR Inhibitor comprising everolimus or temsirolimus. In certain embodiments, the second therapeutic agent is a MEK Inhibitor. In certain embodiments, the second therapeutic agent is a MEK Inhibitor comprising cobimetinib or trametinib. In certain embodiments, the second therapeutic agent is a MELK Inhibitor. In certain embodiments, the second therapeutic agent is a MELK Inhibitor comprising ARN-7016, APTO-500, or OTS-167. In certain embodiments, the second therapeutic agent is a MTH1

Inhibitor. In certain embodiments, the second therapeutic agent is a MTH1 Inhibitor comprising (S)-crizotinib, TH287, or TH588.

[0198] In certain embodiments, the second therapeutic agent is a PARP Inhibitor. In certain embodiments, the second therapeutic agent is a PARP Inhibitor comprising MP-124, BGB-290, talazoparib, veliparib, niraparib, E7449, rucaparib, or ABT-767. In certain embodiments, the second therapeutic agent is a Phosphoinositide 3-Kinase Inhibitor. In certain embodiments, the second therapeutic agent is a Phosphoinositide 3-Kinase Inhibitor comprising idelalisib. In certain embodiments, the second therapeutic agent is an inhibitor of both PARP1 and DHODH (i.e., an agent that inhibits both poly ADP ribose polymerase 1 and dihydroorotate dehydrogenase).

[0199] In certain embodiments, the second therapeutic agent is a Proteasome Inhibitor. In certain embodiments, the second therapeutic agent is a Proteasome Inhibitor comprising bortezomib or carfilzomib. In certain embodiments, the second therapeutic agent is a Topoisomerase-II Inhibitor. In certain embodiments, the second therapeutic agent is a Topoisomerase-II Inhibitor comprising vosaroxin.

[0200] In certain embodiments, the second therapeutic agent is a Tyrosine Kinase Inhibitor. In certain embodiments, the second therapeutic agent is a Tyrosine Kinase Inhibitor comprising bosutinib, cabozantinib, imatinib or ponatinib. In certain embodiments, the second therapeutic agent is a VEGFR Inhibitor. In certain embodiments, the second therapeutic agent is a VEGFR Inhibitor comprising regorafenib. In certain embodiments, the second therapeutic agent is a WEE1 Inhibitor. In certain embodiments, the second therapeutic agent is a WEE1 Inhibitor comprising AZD1775.

[0201] In some embodiments, the second therapeutic agent is a compound targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK/pan-JAK, FAK, PDK1, PKB/Akt, Ras/MAPK, PI3K, SYK, TYK2, BTK and TEC family, and/or members of the cyclin-dependent kinase family (CDK) including staurosporine derivatives, such as midostaurin; examples of further compounds include UCN-01, safinolol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofofosine; RO 318220 and RO 320432; GO 6976; Isp 3521; LY333531/LY379196;

isochinoline compounds; FTIs; PD184352 or QAN697 (a P13K inhibitor) or AT7519 (CDK inhibitor).

[0202] In certain embodiments, the second therapeutic agent is an agonist of OX40, CD137, CD40, GITR, CD27, HVEM, TNFRSF25, or ICOS. In certain embodiments, the second therapeutic agent is an agonist of OX40, CD137, CD40, or GITR. In certain embodiments, the second therapeutic agent is an agonist of CD27, HVEM, TNFRSF25, or ICOS.

[0203] In certain embodiments, the second therapeutic agent is a therapeutic antibody. In certain embodiments, the therapeutic antibody targets one of the following: CD20, CD30, CD33, CD52, EpCAM, CEA, gpA33, a mucin, TAG-72, CAIX, PSMA, a folate-binding protein, a ganglioside, Le, VEGF, VEGFR, VEGFR2, integrin $\alpha V\beta 3$, integrin $\alpha 5\beta 1$, EGFR, ERBB2, ERBB3, MET, IGF1R, EPHA3, TRAILR1, TRAILR2, RANKL, FAP, tenascin, CD19, KIR, NKG2A, CD47, CEACAM1, c-MET, VISTA, CD73, CD38, BAFF, interleukin-1 beta, B4GALNT1, interleukin-6, and interleukin-6 receptor. In certain embodiments, the therapeutic antibody target CD38. In certain embodiments, the therapeutic antibody is an anti-CD38 antibody.

[0204] In certain embodiments, the second therapeutic agent is selected from the group consisting of rituximab, ibritumomab tiuxetan, tositumomab, obinutuzumab, ofatumumab, brentuximab vedotin, gemtuzumab ozogamicin, alemtuzumab, IGN101, adecatumumab, labetuzumab, huA33, pemtumomab, oregovomab, minetumomab, cG250, J591, Mov18, farletuzumab, 3F8, ch14.18, KW-2871, hu3S193, IgN311, bevacizumab, IM-2C6, pazopanib, sorafenib, axitinib, CDP791, lenvatinib, ramucirumab, etaracizumab, volociximab, cetuximab, panitumumab, nimotuzumab, 806, afatinib, erlotinib, gefitinib, osimertinib, vandetanib, trastuzumab, pertuzumab, MM-121, AMG 102, METMAB, SCH 900105, AVE1642, IMC-A12, MK-0646, R1507, CP 751871, KB004, IIIA-4, mapatumumab, HGS-ETR2, CS-1008, denosumab, sibrotuzumab, F19, 81C6, MEDI551, lirilumab, MEDI9447, daratumumab, belimumab, canakinumab, dinutuximab, siltuximab, and tocilizumab.

[0205] In certain embodiments, the second therapeutic agent is a therapeutic antibody targeting EGFR. In certain embodiments, the therapeutic antibody targeting EGFR is selected from cetuximab, matuzumab, panitumumab, and necitumumab. In certain embodiments, the therapeutic antibody targeting EGFR is selected from Mab A13, AMG595, cetuximab (Erbix, C225), depatuxizumab (ABT 806), depatuxizumab, mafodotin, duligotuzumab (MEHD7945A,

RG7597), Futuximab (Sym004), GC1118, imgatuzumab (GA201), matuzumab (EMD 72000), necitumumab (Portrazza), nimotuzumab (h-R3), anitumumab (Vectibix, ABX-EGF), zalutumumab, humMR1, and tomuzotuximab.

[0206] In certain embodiments, the second therapeutic agent is a cytokine. In certain embodiments, the cytokine is IL-12, IL-15, IL-2, IL-18, GM-CSF, or G-CSF.

[0207] In certain embodiments, the second therapeutic agent is sipuleucel-T, aldesleukin (a human recombinant interleukin-2 product having the chemical name des-alanyl-1, serine-125 human interleukin-2), dabrafenib (a kinase inhibitor having the chemical name *N*-{3-[5-(2-aminopyrimidin-4-yl)-2-*tert*-butyl-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide), vemurafenib (a kinase inhibitor having the chemical name propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide), or 2-chloro-deoxyadenosine.

[0208] In certain embodiments, the second therapeutic agent is a placental growth factor, an antibody-drug conjugate, an oncolytic virus, or a therapeutic vaccine. In certain embodiments, the second therapeutic agent is a placental growth factor. In certain embodiments, the second therapeutic agent is a placental growth factor comprising ziv-aflibercept. In certain embodiments, the second therapeutic agent is an antibody-drug conjugate. In certain embodiments, the second therapeutic agent is an antibody-drug conjugate selected from the group consisting of brentoxumab vedotin and trastuzumab emtransine.

[0209] In certain embodiments, the second therapeutic agent is an oncolytic virus. In certain embodiments, the second therapeutic agent is the oncolytic virus talimogene laherparepvec. In certain embodiments, the second therapeutic agent is a therapeutic vaccine. In certain embodiments, the second therapeutic agent is a therapeutic vaccine selected from the group consisting of a GM-CSF tumor vaccine, a STING/GM-CSF tumor vaccine, and NY-ESO-1. In certain embodiments, the second therapeutic agent is a cytokine selected from IL-12, IL-15, GM-CSF, and G-CSF.

[0210] In certain embodiments, the second therapeutic agent is an immune checkpoint inhibitor (also referred to as immune checkpoint blockers). Immune checkpoint inhibitors are a class of therapeutic agents that have the effect of blocking immune checkpoints. See, for example, Pardoll in *Nature Reviews Cancer* (2012) vol. 12, pages 252-264. In certain embodiments, the

immune checkpoint inhibitor is an agent that inhibits one or more of (i) cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), (ii) programmed cell death protein 1 (PD-1), (iii) PD-L1, (iv) LAB3, (v) B7-H3, (vi) B7-H4, (vii) TIM3, (viii) IDO, (ix) LAG-3, (x) T cell immunoglobulin and ITIM domain (TIGIT), (xi) T cell immunoglobulin and mucin-domain containing-3 (TIM-3), (xii) indoleamine 2,3-dioxygenase (IDO), (xiii) CD39, (xiv) NKG2A, (xv) signal regulatory protein alpha (SIRP α), (xvi) inducible T cell costimulator (ICOS), (xvii) glucocorticoid-induced TNF receptor family-related protein (GITR), (xviii) TNF receptor superfamily member 4 (OX40), (xix) TNF receptor superfamily member 9 (4-1BB), and (xx) Toll-like receptors (TLRs). In certain embodiments, the immune checkpoint inhibitor is ipilimumab. In certain embodiments, the immune checkpoint inhibitor is pembrolizumab. In certain embodiments, the immune checkpoint inhibitor is cemiplimab. In certain embodiments, the immune checkpoint inhibitor is atezolizumab. In certain embodiments, the immune checkpoint inhibitor is avelumab. In certain embodiments, the immune checkpoint inhibitor is durvalumab.

[0211] In certain embodiments, the immune checkpoint inhibitor is relatlimab-rmbw, MK-4280, REGN3767, MGD013, sabatolimab (MBG453), or epacadostat. In certain embodiments, the immune checkpoint inhibitor is margetuximab, retifanlimab, trastuzumab, favezelimab, regorafenib, fianlimab, cemiplimab, BGB-A317, tiragolumab, zimberelimab, domvanalimab, ociperlimab, or feladilimab.

[0212] In certain embodiments, the second therapeutic agent is a monoclonal antibody that targets a non-checkpoint target (e.g., herceptin or amivantamab). In certain embodiments, the second therapeutic agent is a non-cytotoxic agent (e.g., a tyrosine-kinase inhibitor).

[0213] In certain embodiments, the second therapeutic agent is selected from mitomycin, ribomustin, vincristine, tretinoin, etoposide, cladribine, gemcitabine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, cytarabine, bicalutamide, vinorelbine, vesnarinone, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, colony

stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, leutinizing hormone releasing factor, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma.

[0214] In certain embodiments, the second therapeutic agent is radiation therapy. In certain embodiments, the second therapeutic agent is Pluvicto, Xofigo, or Lutathera. In certain embodiments, the second therapeutic agent is selected from radionuclide therapies targeting PSMA, SSTR, FAP, FGFR3, CCK2, CD46, or IGF-1R with auger, alpha or beta particles.

[0215] In certain embodiments, the second therapeutic agent is a PRMT5 inhibitor. In certain embodiments, the second therapeutic agent is AMG193, TNG908, GSK3326595, JNJ-64619187, PF-06939999, PRT811, or MRTX1719. In certain embodiments, the second therapeutic agent is AMG193. In certain embodiments, the second therapeutic agent is TNG908. In certain embodiments, the second therapeutic agent is GSK3326595. In certain embodiments, the second therapeutic agent is JNJ-64619187. In certain embodiments, the second therapeutic agent is PF-06939999. In certain embodiments, the second therapeutic agent is PRT811. In certain embodiments, the second therapeutic agent is MRTX1719.

[0216] In certain embodiments, the second therapeutic agent is a MEK Inhibitor. In certain embodiments, the second therapeutic agent is binimetinib, cobimetinib, refametinib, selumetinib, trametinib, or a pharmaceutically acceptable salt and/or solvate of any of the foregoing. In certain embodiments, the second therapeutic agent is binimetinib, cobimetinib, selumetinib, trametinib, or a pharmaceutically acceptable salt and/or solvate of any of the foregoing.

[0217] In certain embodiments, the second therapeutic agent is trametinib or a pharmaceutically acceptable salt and/or solvate thereof. In certain embodiments, the second therapeutic agent is trametinib or a pharmaceutically acceptable solvate thereof. In certain embodiments, the second therapeutic agent is trametinib dimethylsulfoxide. In certain embodiments, the second therapeutic agent is trametinib.

[0218] In certain embodiments, the second therapeutic agent is binimetinib or a pharmaceutically acceptable salt and/or solvate thereof. In certain embodiments, the second therapeutic agent is cobimetinib or a pharmaceutically acceptable salt and/or solvate thereof. In certain embodiments, the second therapeutic agent is refametinib or a pharmaceutically acceptable salt and/or solvate

thereof. In certain embodiments, the second therapeutic agent is selumetinib or a pharmaceutically acceptable salt and/or solvate thereof.

[0219] In certain embodiments, the second therapeutic agent is binimetinib. In certain embodiments, the second therapeutic agent is cobimetinib. In certain embodiments, the second therapeutic agent is refametinib. In certain embodiments, the second therapeutic agent is selumetinib.

[0220] In certain embodiments, the second therapeutic agent is a PARP inhibitor. In certain embodiments, the second therapeutic agent is olaparib, rucaparib, talazoparib, or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is olaparib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is olaparib. In certain embodiments, the second therapeutic agent is rucaparib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is rucaparib. In certain embodiments, the second therapeutic agent is talazoparib or a pharmaceutically acceptable salt thereof. In certain embodiments, the second therapeutic agent is talazoparib.

[0221] In certain embodiments, the second therapeutic agent is an androgen receptor degrader. In certain embodiments, the second therapeutic agent is ARV-766.

[0222] In certain embodiments, the second therapeutic agent is a radioligand therapy agent. In certain embodiments, the second therapeutic agent is lutetium Lu 177 vipivotide tetraxetan (which is marketed at PLUVICTO®).

Subject

[0223] In certain embodiments, the subject is a human. In certain embodiments, the subject is an adult human. In certain embodiments, the subject is a pediatric human. In certain embodiments, the subject is a companion animal. In certain embodiments, the subject is a canine, feline, or equine.

[0224] In certain embodiments, the subject has a translocation t(4;14). In certain embodiments, the subject has a Gain of Function mutation in multiple myeloma SET domain (MMSET).

Outcome Measures

[0225] In some embodiments of the methods and uses described herein, a cancer is treated by inhibiting or reducing or decreasing or arresting further growth or spread of the cancer or tumor. In some embodiments of the methods and uses described herein, a cancer is treated by inhibiting or reducing the size (e.g., volume or mass) of the cancer or tumor by at least 5%, at least 10%, at least 25%, at least 50%, at least 75%, at least 90% or at least 99% relative to the size of the cancer or tumor prior to treatment. In some embodiments of the methods and uses described herein, a cancer is treated by reducing the quantity of the cancers or tumors in the patient by at least 5%, at least 10%, at least 25%, at least 50%, at least 75%, at least 90% or at least 99% relative to the quantity of the cancers or tumors prior to treatment.

Medical Use

[0226] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I) in the manufacture of a medicament. In certain embodiments, the medicament is for treating a disorder described herein, such as cancer.

[0227] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I) for treating a medical disorder, such as a medical disorder described herein, such as cancer.

[0228] Another aspect of the invention provides a compound described herein (such as a compound of Formula I) for use in treating a medical disorder, such as a medical disorder described herein, such as cancer.

General Considerations for Combination Therapy

[0229] In some embodiments, the method includes co-administering the first therapeutic agent and the second therapeutic agent. In some embodiments, the first therapeutic agent and the second therapeutic agent are administered sequentially. In some embodiments, the combination acts synergistically.

[0230] The first therapeutic agent and the second therapeutic agent may be administered as part of a multiple dosage regimen. If administered as a multiple dosage regime, the first therapeutic agent and the second therapeutic agent may be administered simultaneously, sequentially or within a period of time from one another, for example within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 18, 20, 21, 22, 23, or 24 hours from one another. In some embodiments,

the first therapeutic agent and the second therapeutic agent are administered as a multiple dosage regimen more than 24 hours apart.

[0231] As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention.

II. Pharmaceutical Compositions and Dosing Considerations

[0232] As indicated above, the invention provides pharmaceutical compositions, which comprise a therapeutically-effective amount of one or more of the compounds described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. The pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally. In certain embodiments, the invention provides a pharmaceutical composition comprising a compound described herein (*e.g.*, a compound of Formula I) and a pharmaceutically acceptable carrier.

[0233] The phrase “therapeutically effective amount” as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

[0234] The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0235] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0236] Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0237] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

[0238] In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, *e.g.*, bile acids, and polymeric carriers, *e.g.*, polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

[0239] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0240] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

[0241] In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules, trouches and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as crospovidone or ethyl cellulose. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0242] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or

dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0243] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, *e.g.*, freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0244] Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0245] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0246] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters,

microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0247] Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[0248] Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[0249] Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[0250] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0251] Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0252] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by

either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[0253] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[0254] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0255] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0256] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0257] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a

parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0258] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[0259] When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0260] The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

[0261] The phrases “parenteral administration” and “administered parenterally” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0262] The phrases “systemic administration,” “administered systemically,” “peripheral administration” and “administered peripherally” as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient’s system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0263] These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[0264] Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

[0265] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0266] The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0267] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0268] In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Preferably, the compounds are administered at about 0.01 mg/kg to about 200 mg/kg, more preferably at about 0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg.

When the compounds described herein are co-administered with another agent (*e.g.*, as sensitizing agents), the effective amount may be less than when the agent is used alone.

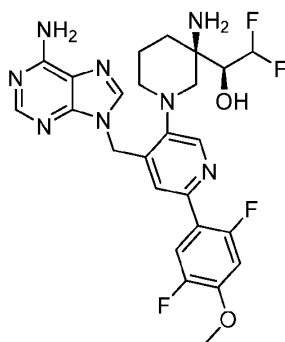
[0269] If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. Preferred dosing is one administration per day.

EXAMPLES

[0270] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention. Starting materials described herein can be obtained from commercial sources or may be readily prepared from commercially available materials using transformations known to those of skill in the art.

EXAMPLE 1 – Evaluation of Impact of Compound I-1 on Cell Adhesion

[0271] The effect of compound I-1 on cell adhesion was evaluated *in vitro* in a KMS11 Adhesion Assay. Test cells (KMS11 cells) were exposed to vehicle (DMS) or compound I-1 for a period of 7 days or 11 days at the following concentration of compound I-1: 0.5 μ M, 1 μ M, 1.5 μ M, or 2.5 μ M. Compound I-1 has the following chemical structure:



[0272] Results are shown in Figure 1. The results show that compound I-1 caused a decrease in cell adhesion.

EXAMPLE 2 – Evaluation of Anti-cancer Activity for Compound I-1 in Combination with Carfilzomib

[0273] Anti-cancer activity of compound I-1 in combination with carfilzomib was evaluated in an assay by subjecting multiple myeloma cells to compound I-1 in combination with carfilzomib. The compound I-1 and carfilzomib were concurrently administered to the multiple myeloma cells. The multiple myeloma cells were a cell line that was resistant to both carfilzomib and bortezomib.

[0274] In this assay, cells were seeded at a density of 10,000 cells per well and left in an incubator. On the following day, cells were treated according to the plate planification, leaving wells with a final volume of 200 μ L. Compound I-1 and carfilzomib were added concurrently to the cells, and the resultant mixture was incubated for four days. On the day of assessing cell viability, the plate and its contents were equilibrated at room temperature for 30 minutes. Then, equal volumes of CellTiter reagent were added to each well (e.g., for a well containing 200 μ L of medium, 200 μ L of reagent were added). Also, reagent was added to wells containing medium to later remove the background luminescence from the medium. Then, contents were mixed for two minutes to induce cell lysis, and then contents were transferred to a 96-well solid white flat plate. Next, the plate was incubated at room temperature for 10 minutes to stabilize luminescent signal, and then luminescence was recorded with an integration time of 0.25-1 second per well.

[0275] The combination of compound I-1 and carfilzomib showed significant anti-cancer activity. Impact on viability of multiple myeloma cells is shown in the table below and in Figure 2. BLISS score analysis revealed that the combination of compound I-1 and carfilzomib produced a synergistic anti-cancer effect across all concentrations of compound I-1 tested in this assay in combination with carfilzomib. Figure 3 is a graph showing BLISS score analysis.

Concentration of Carfilzomib (nM)	Cell Viability Percent (%)			
	Carfilzomib Only	Carfilzomib + Compound I-1 (0.5 μ M)	Carfilzomib + Compound I-1 (1.0 μ M)	Carfilzomib + Compound I-1 (2.5 μ M)
0.1	100.0	100.0	100.0	100.0
10.0	100.0	91.1	88.7	82.4
50.0	89.3	24.6	21.2	17.6

100.0	16.9	0.9	0.6	0.5
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EXAMPLE 3 – Evaluation of Anti-cancer Activity for Compound I-1 in Combination with Mezigdomide

[0276] Anti-cancer activity of compound I-1 in combination with mezigdomide was evaluated in an assay by subjecting H929 multiple myeloma cells to compound I-1 in combination with mezigdomide. Compound I-1 and mezigdomide were concurrently administered to the multiple myeloma cells. The multiple myeloma cells were a cell line that was resistant to pomalidomide.

[0277] In this assay, cells were seeded at a density of 10,000 cells per well and left in an incubator. On the following day, cells were treated according to the plate planification, leaving wells with a final volume of 200 μ L. Compound I-1 and mezigdomide were added concurrently to the cells, and the resultant mixture was incubated for four days. On the day of assessing cell viability, the plate and its contents were equilibrated at room temperature for 30 minutes. Then, equal volumes of CellTiter reagent were added to each well (e.g., for a well containing 200 μ L of medium, 200 μ L of reagent were added). Also, reagent was added to wells containing medium to later remove the background luminescence from the medium. Then, contents were mixed for two minutes to induce cell lysis, and then contents were transferred to a 96-well solid white flat plate. Next, the plate was incubated at room temperature for 10 minutes to stabilize luminescent signal, and then luminescence was recorded with an integration time of 0.25-1 second per well.

[0278] The combination of compound I-1 and mezigdomide showed significant anti-cancer activity. Impact on viability of multiple myeloma cells is shown in the table below and in Figure 4. BLISS score analysis revealed that the combination of compound I-1 and mezigdomide produced a synergistic anti-cancer effect across all concentrations of compound I-1 tested in this assay in combination with mezigdomide. Figure 5 is a graph showing BLISS score analysis.

Concentration of Mezigdomide (nM)	Cell Viability Percent (%)			
	Mezigdomide Only	Mezigdomide + Compound I-1 (0.5 μ M)	Mezigdomide + Compound I-1 (1.0 μ M)	Mezigdomide + Compound I-1 (2.5 μ M)
0.1	98.9	98.9	98.9	98.9
0.5	90.8	7.4	5.0	4.6
1	76.1	4.9	2.9	2.5
2	73.4	2.5	1.2	0.7
5	64.4	2.4	1.5	1.2
10	61.5	1.9	1.5	1.0
50	56.9	1.3	0.8	0.8
100	51.9	1.2	0.8	0.4

EXAMPLE 4 – Evaluation of Anti-cancer Activity for Compound I-1 in Combination with Mezigdomide – Concurrent versus Sequential Administration of Anti-cancer Compounds

[0279] Anti-cancer activity of compound I-1 in combination with mezigdomide was evaluated in an assay by subjecting H929 multiple myeloma cells to compound I-1 in combination with mezigdomide. In a first experiment, compound I-1 was administered to cells for three days, and then thereafter mezigdomide was administered to cells for two days. In a second experiment, compound I-1 and mezigdomide were concurrently administered to the multiple myeloma cells for four days.

[0280] In this assay, cells were seeded at a density of 10,000 cells per well and left in an incubator. On the following day, cells were treated according to the plate planification, leaving wells with a final volume of 200 μ L. In the first experiment, Compound I-1 and mezigdomide were added concurrently to the cells, and the resultant mixture was incubated for four days. In the second experiment, Compound I-1 was added to the cells the resultant mixture was incubated for three days, and then mezigdomide were added to the cells, and the resultant mixture was incubated for two days. On the day of assessing cell viability, the plate and its contents were equilibrated at room temperature for 30 minutes. Then, equal volumes of CellTiter reagent were added to each well (e.g., for a well containing 200 μ L of medium, 200 μ L of reagent were added). Also, reagent was added to wells containing medium to later remove the background

luminescence from the medium. Then, contents were mixed for two minutes to induce cell lysis, and then contents were transferred to a 96-well solid white flat plate. Next, the plate was incubated at room temperature for 10 minutes to stabilize luminescent signal, and then luminescence was recorded with an integration time of 0.25-1 second per well.

[0281] Results are shown in Figure 6. The results show that concurrent administration of compound I-1 and mezigdomide to the multiple myeloma cells produced a greater anti-cancer effect compared to sequential administration where compound I-1 was administered to cells for three days, and then thereafter mezigdomide was administered to cells for two days.

EXAMPLE 5 – Evaluation of Anti-cancer Activity for Compound I-1 in Combination with Pomalidomide

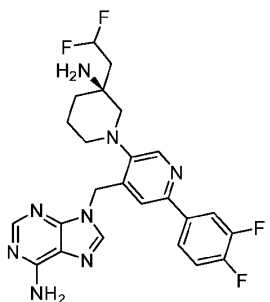
[0282] Anti-cancer activity of compound I-1 in combination with pomalidomide was evaluated in an assay by subjecting H929 multiple myeloma cells to compound I-1 in combination with pomalidomide. The compound I-1 and pomalidomide were concurrently administered to the multiple myeloma cells. The multiple myeloma cells were a cell line that was resistant to pomalidomide.

[0283] The combination of compound I-1 and pomalidomide showed significant anti-cancer activity. Impact on viability of multiple myeloma cells is shown in the table below and in Figure 7. BLISS score analysis revealed that the combination of compound I-1 and pomalidomide produced a synergistic anti-cancer effect across all concentrations of compound I-1 tested in this assay in combination with pomalidomide. Figure 8 is a graph showing BLISS score analysis.

Concentration of Pomalidomide (nM)	Cell Viability Percent (%)			
	Pomalidomide Only	Pomalidomide + Compound I-1 (0.5 μ M)	Pomalidomide + Compound I-1 (1.0 μ M)	Pomalidomide + Compound I-1 (2.5 μ M)
0	92.71	92.71	92.71	92.71
5	84.35	56.95	37.79	33.33
10	75.17	31.44	28.74	26.59
20	60.19	25.37	22.94	17.41
50	53.17	18.49	15.11	11.61
75	48.45	15.11	7.69	2.16
100	13.9	8.64	5.26	1.08

EXAMPLE 6 – Evaluation of Anti-cancer Activity for Compound 47 in Combination with Bortezomib in KMS11 Cell Line Resistant to Carfilzomib and Bortezomib

[0284] Anti-cancer activity of compound 47 in combination with bortezomib was evaluated in an assay by subjecting multiple myeloma cells to compound I-1 in combination with bortezomib. The compound 47 was first administered to the multiple myeloma cells, and then later bortezomib was administered to the multiple myeloma cells. On day 14 after first administration of compound 47, viability of the multiple myeloma cells was evaluated by Cell TiterGlo assay. The multiple myeloma cells were a KMS11 cell line that was resistant to both carfilzomib and bortezomib. Compound 47 has the following chemical structure:



[0285] Experimental procedures are described in more detail below, along with the results.

Part I – Experimental Procedures

[0286] Experimental procedures used to conduct the assay are described in more below:

Step 1: Cell seeding

[0287] Cells were harvested from flasks, placed into fresh cell culture medium, and the cell number counted. The cells were diluted in culture medium and 135 μ L of the cell suspension was added into each well of 96-well cell culture plates. The seeding density of KMS-11 cells resistant to carfilzomib and bortezomib was 200 cells/well. The plates were covered with a lid and placed in 37°C, 5% CO₂ incubator.

Step 2: Compound Preparation

[0288] Stock solutions containing compound 47 at a concentration of 5 mM, 1 mM, 0.6 mM, 0.3 mM, and 0.1 mM were prepared using DMSO as diluent. Stock solutions containing bortezomib at a concentration of 60 μ M, 20 μ M, 13 μ M, 6 μ M, 3 μ M, 2 μ M, 0.6 μ M, 0.2 μ M, 0.06 μ M were prepared using DMSO as diluent. The compound intermediate plate (10X) was prepared. 2 μ L compound solution was diluted in 198 μ L of culture medium. The compound intermediate plate was centrifuged at 1000 rpm for 1 minute and agitated on a microplate shaker for 2 minutes.

Step 3: Compound Treatment

[0289] The medium for cells treated with Compound 47 was half-renewed on day 4 and day 8. The medium containing Compound 47 was half-renewed and added bortezomib (2x) into wells as designed on Day 11. The final concentrations of bortezomib were 0 nM, 0.03 nM, 0.1 nM, 0.3 nM, 1 nM, 1.5 nM, 3 nM, 6.5 nM, 10 nM, and 30 nM. The 96-well plates were cultured in a 5% CO₂ incubator at 37°C.

Step 4: Plate Reading

[0290] After incubating the plates for 14 days, the plates were removed from the incubator and equilibrated at room temperature for 15 minutes. The CellTiter-Glo reagents were thawed at 4°C overnight or by incubating at 37°C before the experiment. The buffer was equilibrated to room temperature and used to dissolve the substrate. 100 μ L of CellTiter-Glo reagents were added into each well, yielding a 1:1 Glo reagent to medium ratio. The plates were shaken on an

orbital shaker for 2 min. Then the plates were placed at room temperature for 10 min followed by reading on a microplate reader.

Step 5: Data Analysis

[0291] Percent inhibition and IC₅₀ values were determined.

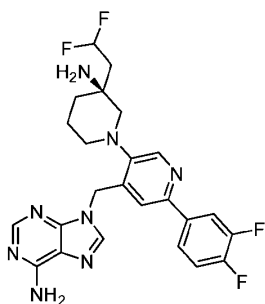
Part II – Results

[0292] The combination of 47 and bortezomib showed significant anti-cancer activity. Impact on viability of multiple myeloma cells is shown in the table below and in Figure 9. BLISS score analysis revealed that the combination of compound 47 and bortezomib produced a synergistic anti-cancer effect. Figure 10 is a graph showing BLISS score analysis.

<u>Test Agent(s)</u>	<u>IC₅₀ (nM)</u>	<u>Max Inhibition (%)</u>
Bortezomib only	28.4	50.6
Compound 47 only	1327	89.4
Bortezomib + 100 nM Compound 47	36.7	41.8
Bortezomib + 300 nM Compound 47	31.3	53.0
Bortezomib + 600 nM Compound 47	1.5	67.5
Bortezomib + 1000 nM Compound 47	2.3	73.9

EXAMPLE 7 – Evaluation of Anti-cancer Activity for Compound 47 in Combination with Carfilzomib in KMS11 Cell Line Sensitive to Carfilzomib and Bortezomib

[0293] Anti-cancer activity of compound 47 in combination with carfilzomib was evaluated in an assay by subjecting multiple myeloma cells to compound 47 in combination with carfilzomib. The compound 47 was first administered to the multiple myeloma cells, and then later carfilzomib was administered to the multiple myeloma cells. The multiple myeloma cells were a KMS11 cell line that was sensitive to both carfilzomib and bortezomib. Compound 47 has the following chemical structure:



[0294] Experimental procedures are described in more detail below, along with the results.

Part I – Experimental Procedures

[0295] Experimental procedures used to conduct the assay are described in more below:

Step 1: Cell seeding

[0296] Cells were harvested from flasks, placed into fresh cell culture medium, and the cell number counted. The cells were diluted in culture medium and 90 μ L of the cell suspension was added into each well of 96-well cell culture plates. The seeding density of KMS-11 cells sensitive to carfilzomib and bortezomib was 200 cells/well. The plates were covered with a lid and placed in 37°C, 5% CO₂ incubator.

Step 2: Compound Preparation

[0297] Stock solutions containing compound 47 at a concentration of 5 mM, 1 mM, 0.6 mM, 0.3 mM, and 0.1 mM were prepared using DMSO as diluent. Stock solutions containing carfilzomib at a concentration of 60 μ M, 20 μ M, 13 μ M, 6 μ M, 3 μ M, 2 μ M, 0.6 μ M, 0.2 μ M, 0.06 μ M were prepared using DMSO as diluent. The compound intermediate plate (10X) was prepared. 2 μ L compound solution was diluted in 198 μ L of culture medium. The compound intermediate plate was centrifuged at 1000 rpm for 1 minute and agitated on a microplate shaker for 2 minutes.

Step 3: Compound Treatment

[0298] The medium for cells treated with Compound 47 was half-renewed on day 4 and day 8. The medium containing Compound 47 was half-renewed and added carfilzomib (2x) into wells as designed on Day 11. The final concentrations of carfilzomib were 0 nM, 0.03 nM, 0.1

nM, 0.3 nM, 1 nM, 1.5 nM, 3 nM, 6.5 nM, 10 nM, and 30 nM. The 96-well plates were cultured in a 5% CO₂ incubator at 37°C.

Step 4: Plate Reading

[0299] After incubating the plates for 14 days, the plates were removed from the incubator and equilibrated at room temperature for 15 minutes. The CellTiter-Glo reagents were thawed at 4°C overnight or by incubating at 37°C before the experiment. The buffer was equilibrated to room temperature and used to dissolve the substrate. 100 µL of CellTiter-Glo reagents were added into each well, yielding a 1:1 Glo reagent to medium ratio. The plates were shaken on an orbital shaker for 2 min. Then the plates were placed at room temperature for 10 min followed by reading on a microplate reader.

Step 5: Data Analysis

[0300] Percent inhibition and IC₅₀ values were determined.

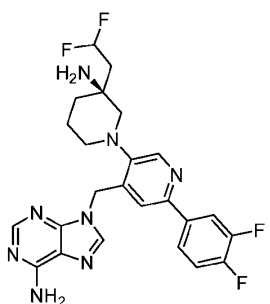
Part II – Results

[0301] The combination of 47 and carfilzomib showed significant anti-cancer activity. Impact on viability of the cells is shown in the table below. BLISS score analysis revealed that the combination of compound I-1 and carfilzomib produced a synergistic anti-cancer. Figure 11 is a graph showing BLISS score analysis.

<u>Test Agent(s)</u>	<u>IC₅₀ (nM)</u>	<u>Max Inhibition (%)</u>
carfilzomib only	15.3	91.7
Compound 47 only	~5104	44.1
carfilzomib + 100 nM Compound 47	11.2	90.2
carfilzomib + 300 nM Compound 47	~10.2	91.2
carfilzomib + 600 nM Compound 47	8.3	97.9
carfilzomib + 1000 nM Compound 47	7.9	99.0
carfilzomib + 5000 nM Compound 47	0.3	>99.9

EXAMPLE 8 – Evaluation of Anti-cancer Activity for Compound 47 in Combination with Carfilzomib in KMS11 Cell Line Resistant to Carfilzomib and Bortezomib

[0302] Anti-cancer activity of compound 47 in combination with carfilzomib was evaluated in an assay by subjecting multiple myeloma cells to compound 47 in combination with carfilzomib. The compound 47 was first administered to the multiple myeloma cells, and then later carfilzomib was administered to the multiple myeloma cells. The multiple myeloma cells were a KMS11 cell line that was resistant to both carfilzomib and bortezomib. Compound 47 has the following chemical structure:



[0303] Experimental procedures are described in more detail below, along with the results.

Part I – Experimental Procedures

[0304] Experimental procedures used to conduct the assay are described in more below:

Step 1: Cell seeding

[0305] Cells were harvested from flasks, placed into fresh cell culture medium, and the cell number counted. The cells were diluted in culture medium and 90 μ L of the cell suspension was added into each well of 96-well cell culture plates. The seeding density of KMS-11 cells resistant to carfilzomib and bortezomib was 200 cells/well. The plates were covered with a lid and placed in 37°C, 5% CO₂ incubator.

Step 2: Compound Preparation

[0306] Stock solutions containing compound 47 at a concentration of 5 mM, 1 mM, 0.6 mM, 0.3 mM, and 0.1 mM were prepared using DMSO as diluent. Stock solutions containing

carfilzomib at a concentration of 60 μ M, 20 μ M, 13 μ M, 6 μ M, 3 μ M, 2 μ M, 0.6 μ M, 0.2 μ M, 0.06 μ M were prepared using DMSO as diluent. The compound intermediate plate (10X) was prepared. 2 μ L compound solution was diluted in 198 μ L of culture medium. The compound intermediate plate was centrifuged at 1000 rpm for 1 minute and agitated on a microplate shaker for 2 minutes.

Step 3: Compound Treatment

[0307] The medium for cells treated with Compound 47 was half-renewed on day 4 and day 8. The medium containing Compound 47 was half-renewed and added carfilzomib (2x) into wells as designed on Day 11. The final concentrations of carfilzomib were 0 nM, 0.03 nM, 0.1 nM, 0.3 nM, 1 nM, 1.5 nM, 3 nM, 6.5 nM, 10 nM, and 30 nM. The 96-well plates were cultured in a 5% CO₂ incubator at 37°C.

Step 4: Plate Reading

[0308] After incubating the plates for 14 days, the plates were removed from the incubator and equilibrated at room temperature for 15 minutes. The CellTiter-Glo reagents were thawed at 4°C overnight or by incubating at 37°C before the experiment. The buffer was equilibrated to room temperature and used to dissolve the substrate. 100 μ L of CellTiter-Glo reagents were added into each well, yielding a 1:1 Glo reagent to medium ratio. The plates were shaken on an orbital shaker for 2 min. Then the plates were placed at room temperature for 10 min followed by reading on a microplate reader.

Step 5: Data Analysis

[0309] Percent inhibition and IC₅₀ values were determined.

Part II – Results

[0310] The combination of 47 and carfilzomib showed significant anti-cancer activity. Impact on viability of the cells is shown in the table below. BLISS score analysis revealed that the combination of compound I-1 and carfilzomib produced a synergistic anti-cancer. Figure 12 is a graph showing BLISS score analysis.

<u>Test Agent(s)</u>	<u>IC₅₀ (nM)</u>	<u>Max Inhibition (%)</u>
carfilzomib only	29.5	51.4
Compound 47 only	2424	77.8
carfilzomib + 100 nM Compound 47	~28.8	63.6
carfilzomib + 300 nM Compound 47	22.3	65.9
carfilzomib + 600 nM Compound 47	20.0	74.2
carfilzomib + 1000 nM Compound 47	14.6	73.3
carfilzomib + 5000 nM Compound 47	<0.01	99.4

INCORPORATION BY REFERENCE

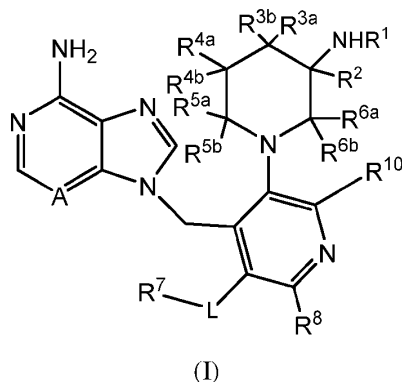
[0311] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0312] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

Claims:

1. A method of treating cancer, comprising administering to a subject in need thereof a therapeutically effective amount of a first therapeutic agent and a second therapeutic agent to treat the cancer, wherein the first therapeutic agent is a compound of Formula I:



or a pharmaceutically acceptable salt thereof; wherein:

A is N or CR⁹ wherein R⁹ is hydrogen or halo;

L is a bond or C₁₋₄ alkylene;

R¹ is H; or

R¹ and R² together with NH forms a 5-8 membered heterocyclyl containing 1-2 heteroatoms selected from N, O and S as ring members; wherein said 5-8 membered heterocyclyl is unsubstituted or substituted by an oxo substituent;

R² is selected from the group consisting of:

(i) hydrogen, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -hydroxyC₁₋₆ alkylene, -hydroxyhaloC₁₋₆ alkylene, -C₁₋₆alkoxyC₁₋₆alkylene, -haloC₁₋₆alkoxyC₁₋₆alkylene or -C₃₋₈ cycloalkoxy(C₁₋₆ alkyl);

(ii) cyano; -cyanoC₁₋₆ alkylene; -C₁₋₆ alkylthioC₁₋₆alkyl; -C₂₋₆ alkenyl; -haloC₂₋₆ alkenyl; -C₂₋₆ alkynyl; -C₁₋₄ alkylSOC₁₋₄alkyl; -C₁₋₄ alkylSO₂C₁₋₄alkyl; -SO₂R⁸ or -C(C₁₋₄ alkyl)=N-O(C₁₋₄ alkyl);

(iii) -C₁₋₄alkylcarbonyl; -(CR^aR^b)_p-C(=O)-OR¹⁰; or -C(=O)-(CR^aR^b)_qR¹¹; wherein R¹¹ is C₃₋₇ cycloalkyl, 5-6 membered heterocyclyl or 5-6 membered heteroaryl, each of which is independently unsubstituted or substituted with C₁₋₆ alkyl or C₁₋₆ alkoxy;

(iv) -(CR^aR^b)_r-C(=O)-NR¹²R¹³ wherein R¹² is hydrogen or C₁₋₆ alkyl; R¹³ is hydrogen, -C₁₋₆ alkyl or a 5-6 membered heterocyclic ring; or R¹² and R¹³ together form a 5-6 membered

heterocyclic ring; wherein said 5-6 membered heterocyclic ring is unsubstituted or substituted with C₁₋₄ alkyl;

(v) 5-6 membered heterocyclylC₀₋₆alkyl or 5-6 membered heterocyclyl(haloC₁₋₄alkyl) wherein each said heterocyclyl radical is unsubstituted or substituted by oxo; and

(vi) 5-9 membered heteroarylC₀₋₆alkyl or 5-9 membered heteroaryl(haloC₁₋₄alkyl), wherein each said heteroaryl radical is unsubstituted or substituted by -C₁₋₄ alkyl, -haloC₁₋₄ alkyl, -hydroxyC₁₋₄ alkylene, -C₁₋₄ alkoxy, -haloC₁₋₄ alkoxy, halo, hydroxy, cyano, oxido, -aminocarbonylC₀₋₆alkyl, -C₁₋₄alkylaminocarbonylC₀₋₆alkyl, -diC₁₋₄alkylaminocarbonylC₀₋₆alkyl or -C₃₋₇ cycloalkyl;

R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^{6a} and R^{6b} are independently hydrogen, halo, cyano, hydroxyl, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -hydroxyC₁₋₆ alkylene, -C₁₋₆ alkoxy, -C₁₋₆alkoxyC₁₋₆alkylene, -haloC₁₋₆ alkoxyC₁₋₆ alkylene, -hydroxyhaloC₁₋₆ alkylene, aryl, -C(=O)-OR¹⁴ or -(CR^aR^b)_s-C(=O)-NR¹⁵R¹⁶; or

R^{3a} and R^{3b}, R^{4a} and R^{4b}, R^{5a} and R^{5b} or R^{6a} and R^{6b} forms an oxo substituent;

R⁷ is H, -C₁₋₄ alkoxy, halo or C₁₋₄ alkyl; or 3-8 membered heterocyclyl, which is unsubstituted or substituted by halo;

R⁸ is C₃₋₈ cycloalkyl(C₀₋₆ alkyl); 4-6 membered heterocyclylC₀₋₆alkyl comprising 1-3 heteroatoms selected from N, O and S; aryl or 5-9 membered heteroarylC₀₋₆alkyl comprising 1-3 heteroatoms selected from N, O and S; wherein R⁸ is unsubstituted or substituted by 1-3 R¹⁷;

R¹⁷ is halo, hydroxy, cyano, -C₁₋₆ alkyl, -haloC₁₋₆ alkyl, -C₁₋₆ alkoxy, -haloC₁₋₆ alkoxy, -NR^aC(=O)CR^c=C(R^c)₂ or -(CR^aR^b)_t-NR^a-C(=O)-R¹⁸;

R^a, R^b, R^c, R¹⁰, R¹⁴, R¹⁵ and R¹⁶ are independently hydrogen or -C₁₋₄ alkyl;

R¹⁸ is -C₁₋₄ alkyl or -C₁₋₄ haloalkyl; and

p, q, r, s and t are independently 0-4; and

the second therapeutic agent is (i) daratumumab, isatuximab, idecabtegene vicleucel, ciltacabtegene autoleucel, or belantamab mafodotin-blmf, (ii) bortezomib, carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, mezigdomide, iberdomide, selinexor, binimetinib, cobimetinib, selumetinib, refametinib, PD-0325901, or ROS126766, or a pharmaceutically acceptable salt thereof, (iii) dacomitinib, mobercitinib, neratinib, osimertinib, or vandetenib, or a pharmaceutically acceptable salt thereof, (iv) a bispecific antibody that binds CD3, (v) a tagged antibody, (vi) a chimeric antigen receptor (CAR) T-

cell therapy cell therapy or a natural killer (NK) cell therapy, (vii) a natural killer cell engager, (viii) a KRAS inhibitor, (ix) an immune checkpoint inhibitor, (x) an FGFR3 inhibitor, (xi) an androgen receptor inhibitor, (xii) a BCL-2, BCLXL, or MCL1 inhibitor, (xiii) PARP inhibitor, (xiv) an androgen receptor degrader, or (xv) a radioligand therapy agent.

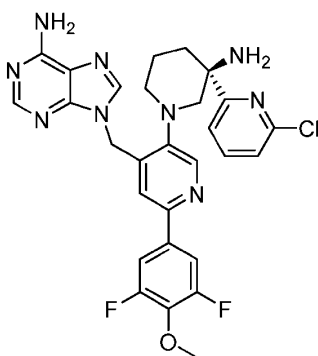
2. The method of claim 1, wherein the second therapeutic agent is daratumumab, isatuximab, idecabtegene viciucl, ciltacabtegene autoleucl, or belantamab mafodotin-blmf.
3. The method of claim 1, wherein the second therapeutic agent is bortezomib, carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, selinexor, binemetinib, cobimetinib, selumetinib, or refametinib, or a pharmaceutically acceptable salt thereof.
4. The method of claim 1, wherein the second therapeutic agent is carfilzomib or a pharmaceutically acceptable salt thereof.
5. The method of claim 1, wherein the second therapeutic agent is mezigdomide or a pharmaceutically acceptable salt thereof.
6. The method of claim 1, wherein the second therapeutic agent is pomalidomide or a pharmaceutically acceptable salt thereof.
7. The method of claim 1, wherein the second therapeutic agent is binemetinib, cobimetinib, or selumetinib, or a pharmaceutically acceptable salt thereof.
8. The method of claim 1, wherein the second therapeutic agent is dacomitinib, mobercitinib, neratinib, osimertinib, or vandetenib, or a pharmaceutically acceptable salt thereof.
9. The method of claim 1, wherein the second therapeutic agent is a bispecific antibody that binds CD3.
10. The method of claim 1, wherein the second therapeutic agent is (i) a bispecific antibody that binds CD3 and BCMA, (ii) a bispecific antibody that binds CD3 and GPRC5D, or (iii) a bispecific antibody that binds CD3 and FcRH5.
11. The method of claim 1, wherein the second therapeutic agent is teclistamab, elrantamab, alnuctamab, lomvoseltamab, ABV-383, HPN-217, talquetamab, forimtamig, cevostamab, or BMS-986393.

12. The method of claim 1, wherein the second therapeutic agent is a tagged antibody.
13. The method of claim 1, wherein the tagged antibody is TAK-573.
14. The method of claim 1, wherein the second therapeutic agent is a chimeric antigen receptor (CAR) T-cell therapy cell therapy or a natural killer (NK) cell therapy.
15. The method of claim 1, wherein the second therapeutic agent is a chimeric antigen receptor (CAR) T-cell therapy cell therapy selected from idecabtagene vicleucel, ciltacabtagene autoleucel, CART-ddBCMA, CT-053, GC012F, MCARH109, or BMS-986393.
16. The method of claim 1, wherein the second therapeutic agent is P-BCMA-ALLO1, ALLO-7715, FT538, FT576, or FT555T.
17. The method of claim 1, wherein the second therapeutic agent is a natural killer cell engager.
18. The method of claim 1, wherein the second therapeutic agent is a natural killer cell engager selected from CYT-338 or CC-92328.
19. The method of claim 1, wherein the second therapeutic agent is a KRAS inhibitor.
20. The method of claim 1, wherein the second therapeutic agent is a KRAS inhibitor selected from sotorasib, adagrasib, JNJ-74699157, LY3499446, LY3537982, GDC-6036, D-1553, JDQ-443, BI 1823911, or AZD4625, or a pharmaceutically acceptable salt thereof.
21. The method of claim 1, wherein the second therapeutic agent is sotorasib or a pharmaceutically acceptable salt thereof.
22. The method of claim 1, wherein the second therapeutic agent is an immune checkpoint inhibitor.
23. The method of claim 1, wherein the second therapeutic agent is an immune checkpoint inhibitor selected from nivolumab and pembrolizumab.
24. The method of claim 1, wherein the second therapeutic agent is an FGFR3 inhibitor.
25. The method of claim 1, wherein the second therapeutic agent is an FGFR3 inhibitor selected from dovitinib, erdafitinib, INCB054828, JNJ-42756493, rogaratinib, or TYRA-300, or a pharmaceutically acceptable salt thereof.

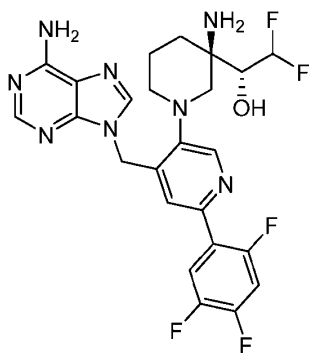
26. The method of claim 1, wherein the second therapeutic agent is an FGFR3 inhibitor that is an anti-FGFR3 antibody selected from PRO-001, B-701, or R3Mab.
27. The method of claim 1, wherein the second therapeutic agent is an androgen receptor inhibitor.
28. The method of claim 1, wherein the second therapeutic agent is an androgen receptor inhibitor selected from apalutamide, enzalutamide, darolutamide, abiraterone, flutamide, and bicalutamide, or a pharmaceutically acceptable salt thereof.
29. The method of claim 1, wherein the second therapeutic agent is a BCL-2, BCLXL, or MCL1 inhibitor, or a pharmaceutically acceptable salt thereof.
30. The method of claim 1, wherein the BCL-2, BCLXL, or MCL1 inhibitor is selected from venetoclax, navitoclax, ABT-737, A-1155463, A-1331852, A64315, AMG397, AMG176, AZD5991, and ABBV467, or a pharmaceutically acceptable salt thereof.
31. The method of any one of claims 1-30, wherein the method further comprises administering to the subject a tyrosine kinase inhibitor.
32. The method of any one of claims 1-30, wherein the method further comprises administering to the subject a tyrosine kinase inhibitor selected from cabozantinib, axitinib, lenvatinib, pazopanib, regorafenib, and sorafenib, or a pharmaceutically acceptable salt thereof.
33. The method of any one of claims 1-32, wherein the method further comprises administering to the subject a PD-1 inhibitor.
34. The method of any one of claims 1-32, wherein the method further comprises administering to the subject a PD-1 inhibitor selected from pembrolizumab, nivolumab, and cemiplimab.
35. The method of any one of claims 1-32, wherein the method further comprises administering to the subject a PD-L1 inhibitor.
36. The method of any one of claims 1-32, wherein the method further comprises administering to the subject a PD-L1 inhibitor selected from atezolizumab, avelumab, and durvalumab.

37. The method of claim 1, wherein the method comprises administering to the subject a therapeutically effective amount of (i) a compound of Formula I or a pharmaceutically acceptable salt thereof, (ii) carfilzomib or a pharmaceutically acceptable salt thereof, and (iii) mezigdomide or a pharmaceutically acceptable salt thereof.
38. The method of any one of claims 1-37, wherein the cancer is multiple myeloma.
39. The method of any one of claims 1-37, wherein the cancer is a solid tumor.
40. The method of any one of claims 1-37, wherein the cancer is a melanoma, carcinoma, neuroblastoma, leukemia, or lymphoma.
41. The method of any one of claims 1-37, wherein the cancer is breast cancer, lung cancer, pancreas cancer, cervical cancer, colorectal cancer, prostate cancer, gastric cancer, skin cancer, liver cancer, bile duct cancer, or nervous system cancer.
42. The method of any one of claims 1-37, wherein the cancer is breast adenocarcinoma, lung adenocarcinoma, pancreas adenocarcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, prostate adenocarcinoma, gastric adenocarcinoma, melanoma, lung squamous cell carcinoma, hepatocellular carcinoma, cholangiocarcinoma, glioblastoma, neuroblastoma, or multiple myeloma.
43. The method of any one of claims 1-37, wherein the cancer is non-small cell lung cancer.
44. The method of any one of claims 1-37, wherein the cancer is acute lymphoblastic leukemia, mantle cell lymphoma, or diffuse large B cell lymphoma.
45. The method of any one of claims 1-44, wherein the cancer is refractory.
46. The method of any one of claims 1-44, wherein the cancer is a relapsed cancer.
47. The method of any one of claims 1-37, wherein the cancer is relapsed, refractory multiple myeloma.
48. The method of any one of claims 1-47, wherein the subject has a translocation t(4;14).
49. The method of any one of claims 1-48, wherein the subject has a Gain of Function mutation in multiple myeloma SET domain (MMSET).
50. The method of any one of claims 1-49, wherein the cancer has a RAS mutation.

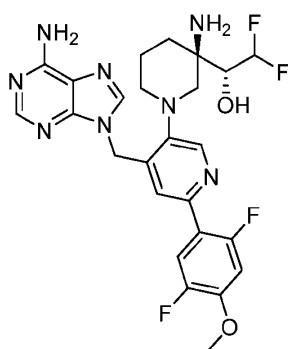
51. The method of any one of claims 1-49, wherein the cancer has a KRAS G12c mutation.
52. The method of any one of claims 1-51, wherein the subject has previously received at least two anti-cancer therapies.
53. The method of any one of claims 1-51, wherein the subject has previously received at least three anti-cancer therapies.
54. The method of any one of claims 1-51, wherein the subject has previously received at least four anti-cancer therapies.
55. The method of any one of claims 52-54, wherein at least one of the prior anti-cancer therapies is a proteasome inhibitor, immunomodulatory drug, immunotherapy antibody, CAR-T therapy, antibody-drug conjugate, bispecific antibody, or MEK inhibitor.
56. The method of any one of claims 52-54, wherein at least one of the prior anti-cancer therapies is carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, daratumumab, isatuximab, idecabtegene vicleucel, ciltacabtegene autoleucel, belantamab mafodotin-blmf, selinexor, binimetinib, cobimetinib, selumetinib, sotorasib, teclistamab, elrantamab, or talquetamab, or a pharmaceutically acceptable salt thereof.
57. The method of any one of claims 1-56, wherein the subject has previously received one prior anti-cancer therapy selected from a proteasome inhibitor, immunomodulatory drug, immunotherapy antibody, CAR-T therapy, antibody therapy, antibody-drug conjugate, XPO1 inhibitor, EGFR inhibitor, KRAS inhibitor, and MEK inhibitor.
58. The method of any one of claims 1-56, wherein the subject has previously received one prior anti-cancer therapy selected from carfilzomib, ixazomib, thalidomide, lenalidomide, pomalidomide, daratumumab, elotuzumab, isatuximab, idecabtegene vicleucel, ciltacabtegene autoleucel, belantamab mafodotin-blmf, selinexor, teclistamab, elrantamab, talquetamab, binimetinib, cobimetinib, selumetinib, sotorasib, osimertinib, erlotinib, gefitinib, dacomitinib, adagrasib, mezigdomide, and iberdomide, or a pharmaceutically acceptable salt thereof.
59. The method of any one of claims 1-58, wherein the subject is a human.
60. The method of any one of claims 1-59, wherein the first therapeutic agent has the following formula or a pharmaceutically acceptable salt thereof:



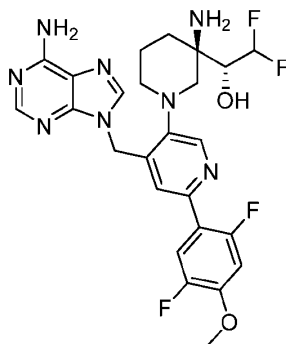
61. The method of any one of claims 1-59, wherein the first therapeutic agent has the following formula or a pharmaceutically acceptable salt thereof:



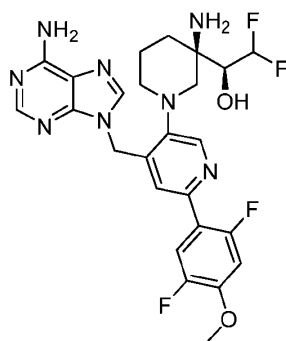
62. The method of any one of claims 1-59, wherein the first therapeutic agent has the following formula or a pharmaceutically acceptable salt thereof:



63. The method of any one of claims 1-59, wherein the first therapeutic agent has the following formula:



64. The method of any one of claims 1-59, wherein the first therapeutic agent has the following formula or a pharmaceutically acceptable salt thereof:



65. The method of any one of claims 1-59, wherein the first therapeutic agent has the following formula:

