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(54) Title: DEUTERIUM-ENRICHED PIPERIDINYL-METHYL-PURINE AMINES AND RELATED COMPOUNDS AND THEIR USE IN TREATING DISEASES AND CONDITIONS

(57) Abstract: The invention provides deuterium-enriched piperidinyl-methyl-purine amines and related compounds, pharmaceutical compositions, their use for inhibiting NSD2, and their use in the treatment of a disease or condition, such as cancer.



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**DEUTERIUM-ENRICHED PIPERIDINYL-METHYL-PURINE AMINES AND
RELATED COMPOUNDS AND THEIR USE IN TREATING DISEASES AND
CONDITIONS**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/296,676 filed on January 5, 2022, the entirety of which is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention provides deuterium-enriched piperidinyl-methyl-purine amines and related compounds, pharmaceutical compositions, their use for inhibiting NSD2, and their use in the treatment of a disease or condition, such as cancer.

BACKGROUND

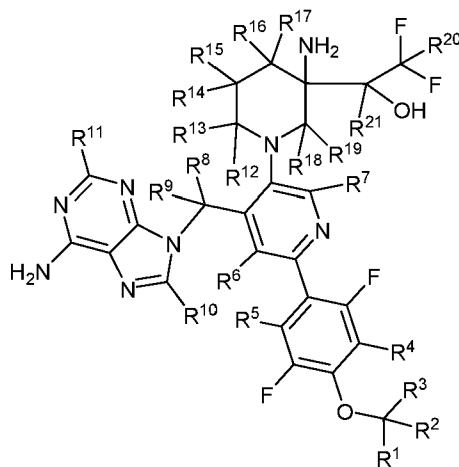
[0003] Cancer continues to be a significant health problem despite the substantial research efforts and scientific advances reported in the literature for treating this disease. Solid tumors, including prostate cancer, breast cancer, and lung cancer remain highly prevalent among the world population. 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 multiple myeloma SET domain (MMSET) or Wolf-Hirschhorn syndrome candidate 1 (WHSC1), is an epigenetic modifier having a role in oncogenesis. Several human cancers are associated with NSD2 overexpression and/or activating point mutations. (Coussens *et al.*, *J. Biol. Chem.* 293 (2018) 13750-13654.) For example, high expression of NSD2 has been reported in human cancers including bladder, brain, gastrointestinal, lung, liver, ovary, skin, uterus, breast, prostate and glioblastoma. Additionally, pediatric cancer genomes appear to be particularly likely to contain NSD2 mutations. Finally, upregulation of NSD2 has been linked with aggressive tumor behavior and poor clinical outcomes. Certain compounds that inhibit NSD2 are described in international patent application publication WO 2021/028854. Additional compounds that inhibit NSD2 would be beneficial to patients suffering from an NSD2-related disease or condition.

[0005] The present invention addresses the foregoing needs and provides other related advantages.

SUMMARY

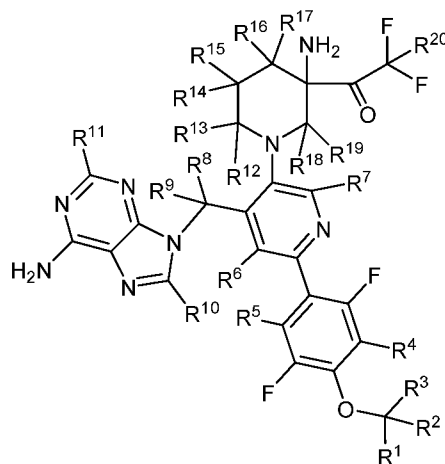
[0006] The invention provides deuterium-enriched piperidinyl-methyl-purine amines and related compounds, pharmaceutical compositions, their use for inhibiting NSD2, and their use in the treatment of a disease or condition, such as cancer. In particular, one aspect of the invention provides a collection of deuterium-enriched piperidinyl-methyl-purine amines and related compounds, such as a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description. Further description of additional collections of deuterium-enriched piperidinyl-methyl-purine amines and related compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0007] Another aspect of the invention provides a collection of difluoromethylketone-substituted piperidinyl-methyl-purine amines and related compounds, including deuterium-enriched compounds, such as a compound represented by Formula II:



(II)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description. Further description of additional collections of difluoromethylketone-substituted piperidiny-methyl-purine amines and related compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0008] Another aspect of the invention provides a method of treating a disease or condition mediated by NSD2 in a subject. The method comprises administering a therapeutically effective amount of a compound described herein, such as a compound of Formula I or II, to a subject in need thereof to treat the disease or condition, as further described in the detailed description.

[0009] Another aspect of the invention provides a method of inhibiting the activity of nuclear SET domain-containing protein 2 (NSD2). The method comprises contacting a NSD2 with an effective amount of a compound described herein, such as a compound of Formula I or II, to inhibit the activity of said NSD2, as further described in the detailed description.

DETAILED DESCRIPTION

[0010] The invention provides deuterium-enriched piperidiny-methyl-purine amines and related compounds, pharmaceutical compositions, their use for inhibiting NSD2, and their use in the treatment of a disease or condition, such as 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.

[0011] Deuterium-enriched refers to the feature that the compound has a quantity of deuterium that is greater than in naturally occurring compounds or synthetic compounds prepared from substrates having the naturally occurring distribution of isotopes. The threshold amount of deuterium enrichment is specified in certain instances in this disclosure, and all percentages given for the amount of deuterium present are mole percentages.

[0012] Deuterium (^2H) is a stable, non-radioactive isotope of ^1H hydrogen and has an atomic weight of 2.014. Hydrogen naturally occurs as a mixture of the isotopes ^1H hydrogen (i.e., protium), deuterium (^2H), and tritium (^3H). The natural abundance of deuterium is 0.015%. One of ordinary skill in the art recognizes that in all chemical compounds with an H atom, the H atom actually represents a mixture of ^1H hydrogen, deuterium (^2H), and tritium (^3H), where about 0.015% is deuterium. Thus, compounds with a level of deuterium that has been enriched to be greater than its natural abundance of 0.015% are considered unnatural and, as a result, novel over their non-enriched counterparts.

[0013] 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.

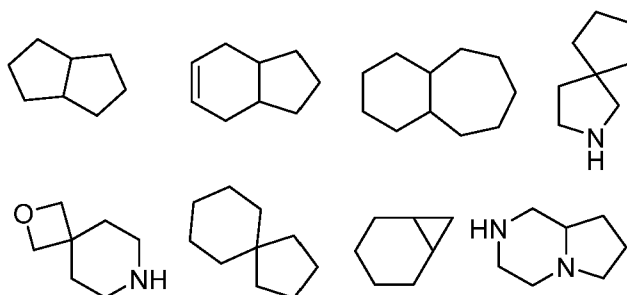
Definitions

[0014] 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.

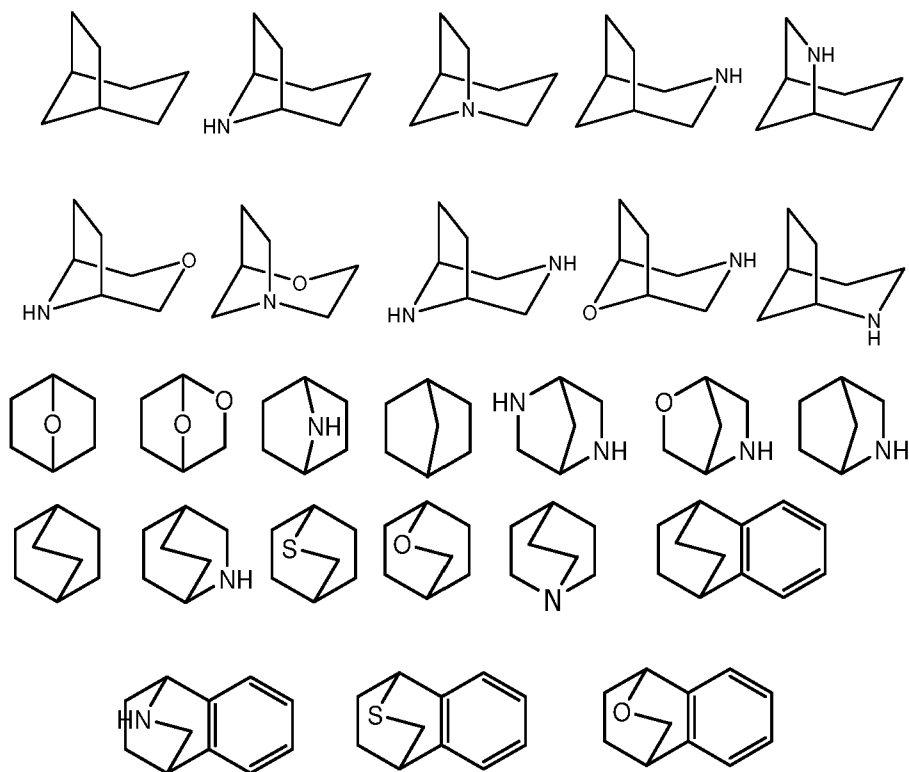
[0015] The term “aliphatic” or “aliphatic group”, as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon 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.

[0016] 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:



[0017] Exemplary bridged bicyclics include:



[0018] 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.

[0019] The term “lower haloalkyl” refers to a C₁₋₄ straight or branched alkyl group that is substituted with one or more halogen atoms.

[0020] 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)).

[0021] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation.

[0022] 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.

[0023] 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

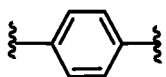
substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0024] 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.

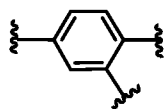
[0025] The term “alkenylene” refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0026] The term “halogen” means F, Cl, Br, or I.

[0027] 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

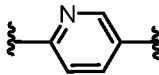


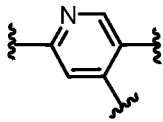
(*e.g.*,). The term “arylene” refers to a bivalent aryl group.

[0028] 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, indolizinyl, 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, cinnolyl, phthalazinyl, quinazolyl, quinoxalyl, 4*H*-quinolizyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolyl, and tetrahydroisoquinolyl. 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.

[0029] The term “heteroarylene” refers to a multivalent heteroaryl group having the appropriate number of open valences to account for groups attached to it. For example, “heteroarylene” is a bivalent heteroaryl group when it has two groups attached to it; “heteroarylene” is a trivalent heteroaryl group when it has three groups attached to it. The term “pyridinylene” refers to a multivalent pyridine radical having the appropriate number of open valences to account for groups attached to it. For example, “pyridinylene” is a bivalent

pyridine radical when it has two groups attached to it (*e.g.*, ); “pyridinylene” is a

trivalent pyridine radical when it has three groups attached to it (*e.g.*, ).

[0030] 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).

[0031] 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,

tetrahydroquinoliny, tetrahydroisoquinoliny, decahydroquinoliny, oxazolidiny, piperaziny, dioxany, dioxolany, diazepiny, oxazepiny, thiazepiny, morpholiny, 2-oxa-6-azaspiro[3.3]heptane, and quinuclidiny. The terms “heterocycle,” “heterocycl,” “heterocycl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocycl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indoliny, 3*H*-indoliny, chromany, phenanthridiny, or tetrahydroquinoliny. A heterocycl group may be mono- or bicyclic. The term “heterocyclalkyl” refers to an alkyl group substituted by a heterocycl, wherein the alkyl and heterocycl portions independently are optionally substituted. The term “oxo-heterocycl” refers to a heterocycl substituted by an oxo group. The term “heterocyclene” refers to a multivalent heterocycl group having the appropriate number of open valences to account for groups attached to it. For example, “heterocyclene” is a bivalent heterocycl group when it has two groups attached to it; “heterocyclene” is a trivalent heterocycl group when it has three groups attached to it.

[0032] 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.

[0033] 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.

[0034] 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; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$, $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-S(O)(NR^\circ)R^\circ$; $-S(O)_2N=C(NR^\circ_2)_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; 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 $-N(R^\circ)_2$.

[0035] 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, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$, $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene)C(O)OR $^\bullet$, or $-SSR^\bullet$.

[0036] Each R^\bullet is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, 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^\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 $=O$, $=S$, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, or a divalent substituent bound to vicinal substitutable carbons of an "optionally substituted" group is $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* 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.

[0037] When R* is C₁₋₆ aliphatic, R* is optionally substituted with halogen, -R[•], -(haloR[•]), -OH, -OR[•], -O(haloR[•]), -CN, -C(O)OH, -C(O)OR[•], -NH₂, -NHR[•], -NR^{•2}, or -NO₂, wherein each R[•] is independently selected from C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, 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.

[0038] An optional substituent on a substitutable nitrogen is independently -R[†], -NR^{†2}, -C(O)R[†], -C(O)OR[†], -C(O)C(O)R[†], -C(O)CH₂C(O)R[†], -S(O)₂R[†], -S(O)₂NR^{†2}, -C(S)NR^{†2}, -C(NH)NR^{†2}, or -N(R[†])S(O)₂R[†]; wherein each R[†] is independently hydrogen, C₁₋₆ aliphatic, unsubstituted -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 R[†], 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 R[†] is C₁₋₆ aliphatic, R[†] is optionally substituted with halogen, -R[•], -(haloR[•]), -OH, -OR[•], -O(haloR[•]), -CN, -C(O)OH, -C(O)OR[•], -NH₂, -NHR[•], -NR^{•2}, or -NO₂, wherein each R[•] is independently selected from C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] 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 an atropisomer (*e.g.*, substituted biaryls), all forms of such atropisomer are considered part of this invention.

[0045] 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.

[0046] Unless specified otherwise, the term “about” refers to within $\pm 10\%$ of the stated value. The invention encompasses embodiments where the value is within $\pm 9\%$, $\pm 8\%$, $\pm 7\%$, $\pm 6\%$, $\pm 5\%$, $\pm 4\%$, $\pm 3\%$, $\pm 2\%$, or $\pm 1\%$ of the stated value.

[0047] The terms “a” and “an” as used herein mean “one or more” and include the plural unless the context is inappropriate.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] The terms “alkoxyl” or “alkoxy” are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxy groups include methoxy, ethoxy, propyloxy, *tert*-butoxy and the like. The term “haloalkoxyl” refers to an alkoxy 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 alkoxy group that is substituted with at least one hydroxyl. Exemplary hydroxyalkoxyl groups include -OCH₂CH₂OH, -OCH₂C(H)(OH)CH₂CH₂OH, and the like. The term “alkoxylene” refers to a bivalent alkoxy group.

[0053] The term “oxo” is art-recognized and refers to a “=O” substituent. For example, a cyclopentane substituted with an oxo group is cyclopentanone.

[0054] The symbol “” indicates a point of attachment.

[0055] 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.

[0056] 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 ethanolates, methanolates, and the like. “Hydrate” is a solvate wherein the solvent molecule is H₂O.

[0057] 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.

[0058] As used herein, the term "compound" refers to a quantity of molecules that is sufficient to be weighed, tested for its structural identity, and to have a demonstrable use (*e.g.*, a quantity that can be shown to be active in an assay, an *in vitro* test, or *in vivo* test, or a quantity that can be administered to a patient and provide a therapeutic benefit).

[0059] Unless indicated otherwise, when a D is specifically recited at a position or is shown in a formula, this D represents a mixture of hydrogen and deuterium where the amount of deuterium is about 100% (*i.e.*, the abundance of deuterium ranges from at least 90% up to 100%). In certain embodiments, the abundance of deuterium in D is from 95% to 100%, or from 97% to 100%. In certain embodiments, the abundance of deuterium in D is at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%.

[0060] The term “IC₅₀” is art-recognized and refers to the concentration of a compound that is required to achieve 50% inhibition of the target.

[0061] 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.

[0062] 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.

[0063] 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*.

[0064] 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].

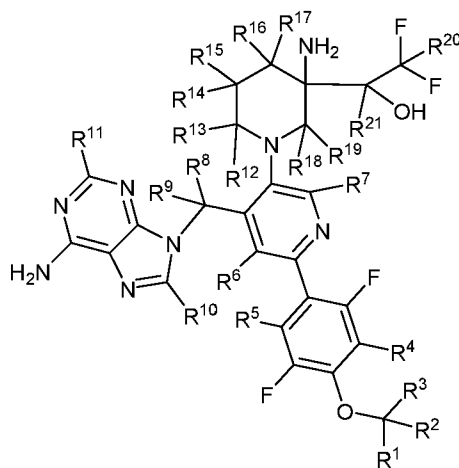
[0065] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention 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.

[0066] As a general matter, compositions specifying a percentage are by weight unless otherwise specified.

I. Deuterium-Enriched Piperidinyl-Methyl-Purine Amines and Related Compounds

[0067] The invention provides deuterium-enriched piperidinyl-methyl-purine amines and related compounds. The compounds may be used in the pharmaceutical compositions and therapeutic methods described herein. Exemplary compounds are described in the following sections, along with exemplary procedures for making the compounds.

[0068] One aspect of the invention provides a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , and R^{21} are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%;

provided that at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , and R^{21} is Z.

[0069] 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).

[0070] In certain embodiments, the compound is a compound of Formula I.

[0071] As defined generally above, R^1 is H or Z. In certain embodiments, R^1 is H. In certain embodiments, R^1 is Z. In certain embodiments, R^1 is selected from the groups depicted in the compounds in Table 1, below.

[0072] As defined generally above, R^2 is H or Z. In certain embodiments, R^2 is H. In certain embodiments, R^2 is Z. In certain embodiments, R^2 is selected from the groups depicted in the compounds in Table 1, below.

[0073] As defined generally above, R^3 is H or Z. In certain embodiments, R^3 is H. In certain embodiments, R^3 is Z. In certain embodiments, R^3 is selected from the groups depicted in the compounds in Table 1, below.

[0074] In certain embodiments, R^1 , R^2 , and R^3 are H. In certain embodiments, R^1 , R^2 , and R^3 are Z.

[0075] As defined generally above, R^4 is H or Z. In certain embodiments, R^4 is H. In certain embodiments, R^4 is Z. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Table 1, below.

[0076] As defined generally above, R^5 is H or Z. In certain embodiments, R^5 is H. In certain embodiments, R^5 is Z. In certain embodiments, R^5 is selected from the groups depicted in the compounds in Table 1, below.

[0077] As defined generally above, R^6 is H or Z. In certain embodiments, R^6 is H. In certain embodiments, R^6 is Z. In certain embodiments, R^6 is selected from the groups depicted in the compounds in Table 1, below.

[0078] As defined generally above, R^7 is H or Z. In certain embodiments, R^7 is H. In certain embodiments, R^7 is Z. In certain embodiments, R^7 is selected from the groups depicted in the compounds in Table 1, below.

[0079] In certain embodiments, R^4 , R^5 , R^6 , and R^7 are H. In certain embodiments, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 are H.

[0080] As defined generally above, R^8 is H or Z. In certain embodiments, R^8 is H. In certain embodiments, R^8 is Z. In certain embodiments, R^8 is selected from the groups depicted in the compounds in Table 1, below.

[0081] As defined generally above, R^9 is H or Z. In certain embodiments, R^9 is H. In certain embodiments, R^9 is Z. In certain embodiments, R^9 is selected from the groups depicted in the compounds in Table 1, below.

[0082] In certain embodiments, R^8 and R^9 are H. In certain embodiments, R^8 and R^9 are Z. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are H. In certain embodiments, R^1 , R^2 , R^3 , R^8 , and R^9 are Z.

[0083] As defined generally above, R^{10} is H or Z. In certain embodiments, R^{10} is H. In certain embodiments, R^{10} is Z. In certain embodiments, R^{10} is selected from the groups depicted in the compounds in Table 1, below.

[0084] As defined generally above, R^{11} is H or Z. In certain embodiments, R^{11} is H. In certain embodiments, R^{11} is Z. In certain embodiments, R^{11} is selected from the groups depicted in the compounds in Table 1, below.

[0085] In certain embodiments, R^{10} and R^{11} are H. In certain embodiments, R^{10} and R^{11} are Z. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^{10} , and R^{11} are H. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11} are H.

[0086] As defined generally above, R^{12} is H or Z. In certain embodiments, R^{12} is H. In certain embodiments, R^{12} is Z. In certain embodiments, R^{12} is selected from the groups depicted in the compounds in Table 1, below.

[0087] As defined generally above, R^{13} is H or Z. In certain embodiments, R^{13} is H. In certain embodiments, R^{13} is Z. In certain embodiments, R^{13} is selected from the groups depicted in the compounds in Table 1, below.

[0088] In certain embodiments, R^{12} and R^{13} are H. In certain embodiments, R^{12} and R^{13} are Z. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^{10} , R^{11} , R^{12} , and R^{13} are H. In certain embodiments, R^1 , R^2 , R^3 , R^8 , R^9 , R^{12} , and R^{13} are Z. In certain embodiments, R^1 , R^2 , R^3 , R^{12} , and R^{13} are Z. In certain embodiments, R^8 , R^9 , R^{12} , and R^{13} are Z.

[0089] As defined generally above, R^{14} is H or Z. In certain embodiments, R^{14} is H. In certain embodiments, R^{14} is Z. In certain embodiments, R^{14} is selected from the groups depicted in the compounds in Table 1, below.

[0090] As defined generally above, R¹⁵ is H or Z. In certain embodiments, R¹⁵ is H. In certain embodiments, R¹⁵ is Z. In certain embodiments, R¹⁵ is selected from the groups depicted in the compounds in Table 1, below.

[0091] As defined generally above, R¹⁶ is H or Z. In certain embodiments, R¹⁶ is H. In certain embodiments, R¹⁶ is Z. In certain embodiments, R¹⁶ is selected from the groups depicted in the compounds in Table 1, below.

[0092] As defined generally above, R¹⁷ is H or Z. In certain embodiments, R¹⁷ is H. In certain embodiments, R¹⁷ is Z. In certain embodiments, R¹⁷ is selected from the groups depicted in the compounds in Table 1, below.

[0093] In certain embodiments, R¹⁴, R¹⁵, R¹⁶, and R¹⁷ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹⁴, R¹⁵, R¹⁶, and R¹⁷ are H.

[0094] As defined generally above, R¹⁸ is H or Z. In certain embodiments, R¹⁸ is H. In certain embodiments, R¹⁸ is Z. In certain embodiments, R¹⁸ is selected from the groups depicted in the compounds in Table 1, below.

[0095] As defined generally above, R¹⁹ is H or Z. In certain embodiments, R¹⁹ is H. In certain embodiments, R¹⁹ is Z. In certain embodiments, R¹⁹ is selected from the groups depicted in the compounds in Table 1, below.

[0096] In certain embodiments, R¹⁸ and R¹⁹ are H. In certain embodiments, R¹², R¹³, R¹⁸, and R¹⁹ are H. In certain embodiments, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, and R¹⁹ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, and R¹⁹ are H.

[0097] In certain embodiments, R¹⁸ and R¹⁹ are Z. In certain embodiments, R¹², R¹³, R¹⁸, and R¹⁹ are Z. In certain embodiments, R¹, R², R³, R¹², R¹³, R¹⁸, and R¹⁹ are Z. In certain embodiments, R⁸, R⁹, R¹², R¹³, R¹⁸, and R¹⁹ are Z. In certain embodiments, R¹, R², R³, R⁸, R⁹, R¹², R¹³, R¹⁸, and R¹⁹ are Z.

[0098] As defined generally above, R²⁰ is H or Z. In certain embodiments, R²⁰ is H. In certain embodiments, R²⁰ is Z. In certain embodiments, R²⁰ is selected from the groups depicted in the compounds in Table 1, below.

[0099] In certain embodiments, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R²⁰ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H.

[0100] In certain embodiments, R¹², R¹³, R¹⁸, R¹⁹, and R²⁰ are Z. In certain embodiments, R¹, R², R³, and R²⁰ are Z. In certain embodiments, R⁸, R⁹, and R²⁰ are Z. In certain embodiments,

$R^1, R^2, R^3, R^{12}, R^{13}, R^{18}, R^{19}$, and R^{20} are Z. In certain embodiments, $R^8, R^9, R^{12}, R^{13}, R^{18}, R^{19}$, and R^{20} are Z. In certain embodiments, $R^1, R^2, R^3, R^8, R^9, R^{12}, R^{13}, R^{18}, R^{19}$, and R^{20} are Z.

[0101] As defined generally above, R^{21} is H or Z. In certain embodiments, R^{21} is H. In certain embodiments, R^{21} is Z. In certain embodiments, R^{21} is selected from the groups depicted in the compounds in Table 1, below.

[0102] In certain embodiments, $R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$, and R^{21} are H. In certain embodiments, $R^4, R^5, R^6, R^7, R^{10}, R^{11}, R^{14}, R^{15}, R^{16}, R^{17}$, and R^{21} are H. In certain embodiments, $R^4, R^5, R^6, R^7, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$, and R^{21} are H.

[0103] In certain embodiments, R^{20} and R^{21} are Z. In certain embodiments, $R^{12}, R^{13}, R^{18}, R^{19}$, and R^{21} are Z. In certain embodiments, R^1, R^2, R^3 , and R^{21} are Z. In certain embodiments, R^8, R^9 , and R^{21} are Z. In certain embodiments, $R^1, R^2, R^3, R^{12}, R^{13}, R^{18}, R^{19}$, and R^{21} are Z. In certain embodiments, $R^8, R^9, R^{12}, R^{13}, R^{18}, R^{19}$, and R^{21} are Z. In certain embodiments, $R^1, R^2, R^3, R^8, R^9, R^{12}, R^{13}, R^{18}, R^{19}$, and R^{21} are Z.

[0104] As defined generally above, Z is hydrogen or deuterium, provided that the abundance of deuterium in Z is at least 75%. In certain embodiments, the abundance of deuterium in Z is at least 80%. In certain embodiments, the abundance of deuterium in Z is at least 85%. In certain embodiments, the abundance of deuterium in Z is at least 90%. In certain embodiments, the abundance of deuterium in Z is at least 95%. In certain embodiments, the abundance of deuterium in Z is at least 97%. In certain embodiments, the abundance of deuterium in Z is at least 99%. In certain embodiments, the abundance of deuterium in Z is about 100%.

[0105] As defined generally above, at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$, and R^{21} is Z. In certain embodiments, one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$, and R^{21} is Z. In certain embodiments, at least two of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$, and R^{21} are Z. In certain embodiments, two of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$, and R^{21} are Z. In certain embodiments, at least three of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$, and R^{21} are Z. In certain embodiments, three of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$, and R^{21} are Z. In certain embodiments, four or five of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$, and R^{21} are Z. In certain embodiments, more than five of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$, and R^{21} are Z.

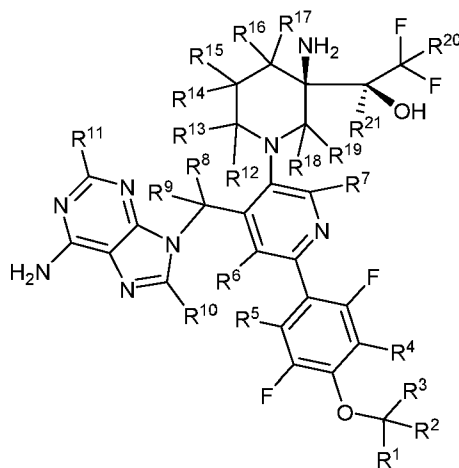
[0106] In certain embodiments, one or more of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , and R^{21} is Z at a position where D is depicted in the compounds in Table 1, below.

[0107] In certain embodiments, the compound has an enantiomeric excess of at least 85%. In certain embodiments, the compound has an enantiomeric excess of at least 90%. In certain embodiments, the compound has an enantiomeric excess of at least 95%. In certain embodiments, the compound has an enantiomeric excess of at least 98%.

[0108] In certain embodiments, the compound has a diastereomeric ratio of at least 10:1. In certain embodiments, the compound has a diastereomeric ratio of at least 15:1. In certain embodiments, the compound has a diastereomeric ratio of at least 20:1. In certain embodiments, the compound has a diastereomeric ratio of at least 50:1. In certain embodiments, the compound has a diastereomeric ratio of at least 100:1.

[0109] The description above describes multiple embodiments relating to compounds of Formula I. The patent application specifically contemplates all combinations of the embodiments.

[0110] Another aspect of the invention provides a compound represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , and R^{21} are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%;

provided that at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , and R^{21} is Z.

[0111] The definitions of variables in Formula I-A 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).

[0112] In certain embodiments, the compound is a compound of Formula I-A.

[0113] As defined generally above, R^1 is H or Z. In certain embodiments, R^1 is H. In certain embodiments, R^1 is Z.

[0114] As defined generally above, R^2 is H or Z. In certain embodiments, R^2 is H. In certain embodiments, R^2 is Z.

[0115] As defined generally above, R^3 is H or Z. In certain embodiments, R^3 is H. In certain embodiments, R^3 is Z.

[0116] In certain embodiments, R^1 , R^2 , and R^3 are H. In certain embodiments, R^1 , R^2 , and R^3 are Z.

[0117] As defined generally above, R^4 is H or Z. In certain embodiments, R^4 is H. In certain embodiments, R^4 is Z.

[0118] As defined generally above, R^5 is H or Z. In certain embodiments, R^5 is H. In certain embodiments, R^5 is Z.

[0119] As defined generally above, R^6 is H or Z. In certain embodiments, R^6 is H. In certain embodiments, R^6 is Z.

[0120] As defined generally above, R^7 is H or Z. In certain embodiments, R^7 is H. In certain embodiments, R^7 is Z.

[0121] In certain embodiments, R^4 , R^5 , R^6 , and R^7 are H. In certain embodiments, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 are H.

[0122] As defined generally above, R^8 is H or Z. In certain embodiments, R^8 is H. In certain embodiments, R^8 is Z.

[0123] As defined generally above, R^9 is H or Z. In certain embodiments, R^9 is H. In certain embodiments, R^9 is Z.

[0124] In certain embodiments, R⁸ and R⁹ are H. In certain embodiments, R⁸ and R⁹ are Z. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are H. In certain embodiments, R¹, R², R³, R⁸, and R⁹ are Z.

[0125] As defined generally above, R¹⁰ is H or Z. In certain embodiments, R¹⁰ is H. In certain embodiments, R¹⁰ is Z.

[0126] As defined generally above, R¹¹ is H or Z. In certain embodiments, R¹¹ is H. In certain embodiments, R¹¹ is Z.

[0127] In certain embodiments, R¹⁰ and R¹¹ are H. In certain embodiments, R¹⁰ and R¹¹ are Z. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, and R¹¹ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are H.

[0128] As defined generally above, R¹² is H or Z. In certain embodiments, R¹² is H. In certain embodiments, R¹² is Z.

[0129] As defined generally above, R¹³ is H or Z. In certain embodiments, R¹³ is H. In certain embodiments, R¹³ is Z.

[0130] In certain embodiments, R¹² and R¹³ are H. In certain embodiments, R¹² and R¹³ are Z. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², and R¹³ are H. In certain embodiments, R¹, R², R³, R⁸, R⁹, R¹², and R¹³ are Z. In certain embodiments, R¹, R², R³, R¹², and R¹³ are Z. In certain embodiments, R⁸, R⁹, R¹², and R¹³ are Z.

[0131] As defined generally above, R¹⁴ is H or Z. In certain embodiments, R¹⁴ is H. In certain embodiments, R¹⁴ is Z.

[0132] As defined generally above, R¹⁵ is H or Z. In certain embodiments, R¹⁵ is H. In certain embodiments, R¹⁵ is Z.

[0133] As defined generally above, R¹⁶ is H or Z. In certain embodiments, R¹⁶ is H. In certain embodiments, R¹⁶ is Z.

[0134] As defined generally above, R¹⁷ is H or Z. In certain embodiments, R¹⁷ is H. In certain embodiments, R¹⁷ is Z.

[0135] In certain embodiments, R¹⁴, R¹⁵, R¹⁶, and R¹⁷ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹⁴, R¹⁵, R¹⁶, and R¹⁷ are H.

[0136] As defined generally above, R¹⁸ is H or Z. In certain embodiments, R¹⁸ is H. In certain embodiments, R¹⁸ is Z. In certain embodiments, R¹⁸ is selected from the groups depicted in the compounds in Table 1, below.

[0137] As defined generally above, R¹⁹ is H or Z. In certain embodiments, R¹⁹ is H. In certain embodiments, R¹⁹ is Z.

[0138] In certain embodiments, R¹⁸ and R¹⁹ are H. In certain embodiments, R¹², R¹³, R¹⁸, and R¹⁹ are H. In certain embodiments, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, and R¹⁹ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, and R¹⁹ are H.

[0139] In certain embodiments, R¹⁸ and R¹⁹ are Z. In certain embodiments, R¹², R¹³, R¹⁸, and R¹⁹ are Z. In certain embodiments, R¹, R², R³, R¹², R¹³, R¹⁸, and R¹⁹ are Z. In certain embodiments, R⁸, R⁹, R¹², R¹³, R¹⁸, and R¹⁹ are Z. In certain embodiments, R¹, R², R³, R⁸, R⁹, R¹², R¹³, R¹⁸, and R¹⁹ are Z.

[0140] As defined generally above, R²⁰ is H or Z. In certain embodiments, R²⁰ is H. In certain embodiments, R²⁰ is Z.

[0141] In certain embodiments, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R²⁰ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H.

[0142] In certain embodiments, R¹², R¹³, R¹⁸, R¹⁹, and R²⁰ are Z. In certain embodiments, R¹, R², R³, and R²⁰ are Z. In certain embodiments, R⁸, R⁹, and R²⁰ are Z. In certain embodiments, R¹, R², R³, R¹², R¹³, R¹⁸, R¹⁹, and R²⁰ are Z. In certain embodiments, R⁸, R⁹, R¹², R¹³, R¹⁸, R¹⁹, and R²⁰ are Z. In certain embodiments, R¹, R², R³, R⁸, R⁹, R¹², R¹³, R¹⁸, R¹⁹, and R²⁰ are Z.

[0143] As defined generally above, R²¹ is H or Z. In certain embodiments, R²¹ is H. In certain embodiments, R²¹ is Z.

[0144] In certain embodiments, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R²¹ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are H.

[0145] In certain embodiments, R²⁰ and R²¹ are Z. In certain embodiments, R¹², R¹³, R¹⁸, R¹⁹, and R²¹ are Z. In certain embodiments, R¹, R², R³, and R²¹ are Z. In certain embodiments, R⁸, R⁹, and R²¹ are Z. In certain embodiments, R¹, R², R³, R¹², R¹³, R¹⁸, R¹⁹, and R²¹ are Z. In certain embodiments, R⁸, R⁹, R¹², R¹³, R¹⁸, R¹⁹, and R²¹ are Z. In certain embodiments, R¹, R², R³, R⁸, R⁹, R¹², R¹³, R¹⁸, R¹⁹, and R²¹ are Z.

[0146] As defined generally above, Z is hydrogen or deuterium, provided that the abundance of deuterium in Z is at least 75%. In certain embodiments, the abundance of deuterium in Z is at least 80%. In certain embodiments, the abundance of deuterium in Z is at least 85%. In certain embodiments, the abundance of deuterium in Z is at least 90%. In certain embodiments, the

abundance of deuterium in Z is at least 95%. In certain embodiments, the abundance of deuterium in Z is at least 97%. In certain embodiments, the abundance of deuterium in Z is at least 99%. In certain embodiments, the abundance of deuterium in Z is about 100%.

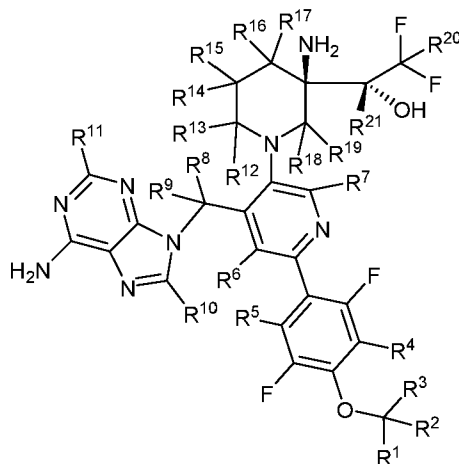
[0147] As defined generally above, at least one of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ is Z. In certain embodiments, one of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ is Z. In certain embodiments, at least two of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are Z. In certain embodiments, two of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are Z. In certain embodiments, at least three of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are Z. In certain embodiments, three of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are Z. In certain embodiments, four or five of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are Z. In certain embodiments, more than five of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are Z.

[0148] In certain embodiments, the compound has an enantiomeric excess of at least 85%. In certain embodiments, the compound has an enantiomeric excess of at least 90%. In certain embodiments, the compound has an enantiomeric excess of at least 95%. In certain embodiments, the compound has an enantiomeric excess of at least 98%.

[0149] In certain embodiments, the compound has a diastereomeric ratio of at least 10:1. In certain embodiments, the compound has a diastereomeric ratio of at least 15:1. In certain embodiments, the compound has a diastereomeric ratio of at least 20:1. In certain embodiments, the compound has a diastereomeric ratio of at least 50:1. In certain embodiments, the compound has a diastereomeric ratio of at least 100:1.

[0150] The description above describes multiple embodiments relating to compounds of Formula I-A. The patent application specifically contemplates all combinations of the embodiments.

[0151] Another aspect of the invention provides a compound represented by Formula I-B:



(I-B)

or a pharmaceutically acceptable salt thereof; wherein:

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%;

provided that at least one of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ is Z.

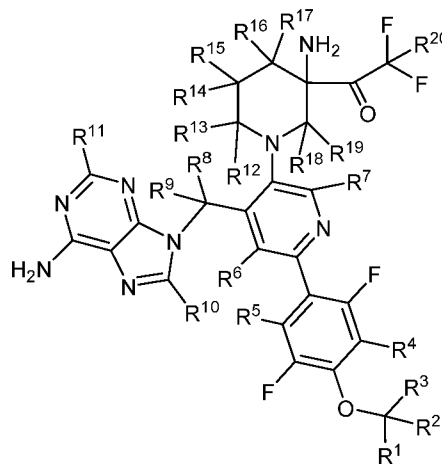
[0152] The definitions of variables in Formula I-B above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition of a variable is 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).

[0153] In certain embodiments, the compound is a compound of Formula I-B.

[0154] In certain embodiments, the present invention provides a compound of Formula I-B, wherein each of the variables is as defined in the description of Formula I-A, above, and described in embodiments herein, both singly and in combination. For example, in certain embodiments, R²¹ is Z. As another example, in certain embodiments, R¹, R², and R³ are Z. As yet another example, in certain embodiments, R¹, R², and R³ are Z; and R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are H.

[0155] The description above describes multiple embodiments relating to compounds of Formula I-B. The patent application specifically contemplates all combinations of the embodiments.

[0156] Another aspect of the invention provides a compound represented by Formula II:



(II)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%.

[0157] The definitions of variables in Formula II 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).

[0158] In certain embodiments, the compound is a compound of Formula II.

[0159] As defined generally above, R^1 is H or Z. In certain embodiments, R^1 is H. In certain embodiments, R^1 is Z. In certain embodiments, R^1 is selected from the groups depicted in the compounds in Table 2, below.

[0160] As defined generally above, R^2 is H or Z. In certain embodiments, R^2 is H. In certain embodiments, R^2 is Z. In certain embodiments, R^2 is selected from the groups depicted in the compounds in Table 2, below.

[0161] As defined generally above, R^3 is H or Z. In certain embodiments, R^3 is H. In certain embodiments, R^3 is Z. In certain embodiments, R^3 is selected from the groups depicted in the compounds in Table 2, below.

[0162] In certain embodiments, R^1 , R^2 , and R^3 are H. In certain embodiments, R^1 , R^2 , and R^3 are Z.

[0163] As defined generally above, R^4 is H or Z. In certain embodiments, R^4 is H. In certain embodiments, R^4 is Z. In certain embodiments, R^4 is selected from the groups depicted in the compounds in Table 2, below.

[0164] As defined generally above, R^5 is H or Z. In certain embodiments, R^5 is H. In certain embodiments, R^5 is Z. In certain embodiments, R^5 is selected from the groups depicted in the compounds in Table 2, below.

[0165] As defined generally above, R^6 is H or Z. In certain embodiments, R^6 is H. In certain embodiments, R^6 is Z. In certain embodiments, R^6 is selected from the groups depicted in the compounds in Table 2, below.

[0166] As defined generally above, R^7 is H or Z. In certain embodiments, R^7 is H. In certain embodiments, R^7 is Z. In certain embodiments, R^7 is selected from the groups depicted in the compounds in Table 2, below.

[0167] In certain embodiments, R^4 , R^5 , R^6 , and R^7 are H. In certain embodiments, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 are H.

[0168] As defined generally above, R^8 is H or Z. In certain embodiments, R^8 is H. In certain embodiments, R^8 is Z. In certain embodiments, R^8 is selected from the groups depicted in the compounds in Table 2, below.

[0169] As defined generally above, R^9 is H or Z. In certain embodiments, R^9 is H. In certain embodiments, R^9 is Z. In certain embodiments, R^9 is selected from the groups depicted in the compounds in Table 2, below.

[0170] In certain embodiments, R^8 and R^9 are H. In certain embodiments, R^8 and R^9 are Z. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are H. In certain embodiments, R^1 , R^2 , R^3 , R^8 , and R^9 are Z.

[0171] As defined generally above, R^{10} is H or Z. In certain embodiments, R^{10} is H. In certain embodiments, R^{10} is Z. In certain embodiments, R^{10} is selected from the groups depicted in the compounds in Table 2, below.

[0172] As defined generally above, R^{11} is H or Z. In certain embodiments, R^{11} is H. In certain embodiments, R^{11} is Z. In certain embodiments, R^{11} is selected from the groups depicted in the compounds in Table 2, below.

[0173] In certain embodiments, R^{10} and R^{11} are H. In certain embodiments, R^{10} and R^{11} are Z. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^{10} , and R^{11} are H. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11} are H.

[0174] As defined generally above, R^{12} is H or Z. In certain embodiments, R^{12} is H. In certain embodiments, R^{12} is Z. In certain embodiments, R^{12} is selected from the groups depicted in the compounds in Table 2, below.

[0175] As defined generally above, R^{13} is H or Z. In certain embodiments, R^{13} is H. In certain embodiments, R^{13} is Z. In certain embodiments, R^{13} is selected from the groups depicted in the compounds in Table 2, below.

[0176] In certain embodiments, R^{12} and R^{13} are H. In certain embodiments, R^{12} and R^{13} are Z. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^{10} , R^{11} , R^{12} , and R^{13} are H. In certain embodiments, R^1 , R^2 , R^3 , R^8 , R^9 , R^{12} , and R^{13} are Z. In certain embodiments, R^1 , R^2 , R^3 , R^{12} , and R^{13} are Z. In certain embodiments, R^8 , R^9 , R^{12} , and R^{13} are Z.

[0177] As defined generally above, R^{14} is H or Z. In certain embodiments, R^{14} is H. In certain embodiments, R^{14} is Z. In certain embodiments, R^{14} is selected from the groups depicted in the compounds in Table 2, below.

[0178] As defined generally above, R^{15} is H or Z. In certain embodiments, R^{15} is H. In certain embodiments, R^{15} is Z. In certain embodiments, R^{15} is selected from the groups depicted in the compounds in Table 2, below.

[0179] As defined generally above, R^{16} is H or Z. In certain embodiments, R^{16} is H. In certain embodiments, R^{16} is Z. In certain embodiments, R^{16} is selected from the groups depicted in the compounds in Table 2, below.

[0180] As defined generally above, R^{17} is H or Z. In certain embodiments, R^{17} is H. In certain embodiments, R^{17} is Z. In certain embodiments, R^{17} is selected from the groups depicted in the compounds in Table 2, below.

[0181] In certain embodiments, R^{14} , R^{15} , R^{16} , and R^{17} are H. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^{10} , R^{11} , R^{14} , R^{15} , R^{16} , and R^{17} are H.

[0182] As defined generally above, R^{18} is H or Z. In certain embodiments, R^{18} is H. In certain embodiments, R^{18} is Z. In certain embodiments, R^{18} is selected from the groups depicted in the compounds in Table 2, below.

[0183] As defined generally above, R¹⁹ is H or Z. In certain embodiments, R¹⁹ is H. In certain embodiments, R¹⁹ is Z. In certain embodiments, R¹⁹ is selected from the groups depicted in the compounds in Table 2, below.

[0184] In certain embodiments, R¹⁸ and R¹⁹ are H. In certain embodiments, R¹², R¹³, R¹⁸, and R¹⁹ are H. In certain embodiments, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, and R¹⁹ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, and R¹⁹ are H.

[0185] In certain embodiments, R¹⁸ and R¹⁹ are Z. In certain embodiments, R¹², R¹³, R¹⁸, and R¹⁹ are Z. In certain embodiments, R¹, R², R³, R¹², R¹³, R¹⁸, and R¹⁹ are Z. In certain embodiments, R⁸, R⁹, R¹², R¹³, R¹⁸, and R¹⁹ are Z. In certain embodiments, R¹, R², R³, R⁸, R⁹, R¹², R¹³, R¹⁸, and R¹⁹ are Z.

[0186] As defined generally above, R²⁰ is H or Z. In certain embodiments, R²⁰ is H. In certain embodiments, R²⁰ is Z. In certain embodiments, R²⁰ is selected from the groups depicted in the compounds in Table 2, below.

[0187] In certain embodiments, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R²⁰ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are H.

[0188] In certain embodiments, R¹², R¹³, R¹⁸, R¹⁹, and R²⁰ are Z. In certain embodiments, R¹, R², R³, and R²⁰ are Z. In certain embodiments, R⁸, R⁹, and R²⁰ are Z. In certain embodiments, R¹, R², R³, R¹², R¹³, R¹⁸, R¹⁹, and R²⁰ are Z. In certain embodiments, R⁸, R⁹, R¹², R¹³, R¹⁸, R¹⁹, and R²⁰ are Z. In certain embodiments, R¹, R², R³, R⁸, R⁹, R¹², R¹³, R¹⁸, R¹⁹, and R²⁰ are Z.

[0189] As defined generally above, Z is hydrogen or deuterium, provided that the abundance of deuterium in Z is at least 75%. In certain embodiments, the abundance of deuterium in Z is at least 80%. In certain embodiments, the abundance of deuterium in Z is at least 85%. In certain embodiments, the abundance of deuterium in Z is at least 90%. In certain embodiments, the abundance of deuterium in Z is at least 95%. In certain embodiments, the abundance of deuterium in Z is at least 97%. In certain embodiments, the abundance of deuterium in Z is at least 99%. In certain embodiments, the abundance of deuterium in Z is about 100%.

[0190] In certain embodiments, at least one of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ is Z. In certain embodiments, one of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ is Z. In certain embodiments, at least two of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are Z. In certain embodiments, two of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are Z. In certain embodiments, at least

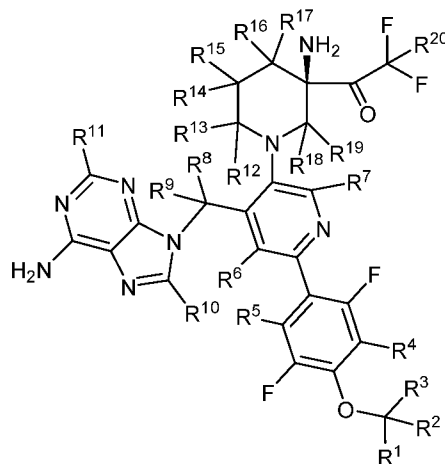
three of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}$, and R^{20} are Z. In certain embodiments, three of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}$, and R^{20} are Z. In certain embodiments, four or five of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}$, and R^{20} are Z. In certain embodiments, more than five of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}$, and R^{20} are Z.

[0191] In certain embodiments, one or more of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}$, and R^{20} is Z at a position where D is depicted in the compounds in Table 2, below.

[0192] In certain embodiments, the compound has an enantiomeric excess of at least 85%. In certain embodiments, the compound has an enantiomeric excess of at least 90%. In certain embodiments, the compound has an enantiomeric excess of at least 95%. In certain embodiments, the compound has an enantiomeric excess of at least 98%.

[0193] The description above describes multiple embodiments relating to compounds of Formula II. The patent application specifically contemplates all combinations of the embodiments.

[0194] Another aspect of the invention provides a compound represented by Formula II-A:



(II-A)

or a pharmaceutically acceptable salt thereof; wherein:

$R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}$, and R^{20} are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%.

[0195] The definitions of variables in Formula II-A 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).

[0196] In certain embodiments, the compound is a compound of Formula II-A.

[0197] As defined generally above, R^1 is H or Z. In certain embodiments, R^1 is H. In certain embodiments, R^1 is Z.

[0198] As defined generally above, R^2 is H or Z. In certain embodiments, R^2 is H. In certain embodiments, R^2 is Z.

[0199] As defined generally above, R^3 is H or Z. In certain embodiments, R^3 is H. In certain embodiments, R^3 is Z.

[0200] In certain embodiments, R^1 , R^2 , and R^3 are H. In certain embodiments, R^1 , R^2 , and R^3 are Z.

[0201] As defined generally above, R^4 is H or Z. In certain embodiments, R^4 is H. In certain embodiments, R^4 is Z.

[0202] As defined generally above, R^5 is H or Z. In certain embodiments, R^5 is H. In certain embodiments, R^5 is Z.

[0203] As defined generally above, R^6 is H or Z. In certain embodiments, R^6 is H. In certain embodiments, R^6 is Z.

[0204] As defined generally above, R^7 is H or Z. In certain embodiments, R^7 is H. In certain embodiments, R^7 is Z.

[0205] In certain embodiments, R^4 , R^5 , R^6 , and R^7 are H. In certain embodiments, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 are H.

[0206] As defined generally above, R^8 is H or Z. In certain embodiments, R^8 is H. In certain embodiments, R^8 is Z.

[0207] As defined generally above, R^9 is H or Z. In certain embodiments, R^9 is H. In certain embodiments, R^9 is Z.

[0208] In certain embodiments, R^8 and R^9 are H. In certain embodiments, R^8 and R^9 are Z. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are H. In certain embodiments, R^1 , R^2 , R^3 , R^8 , and R^9 are Z.

[0209] As defined generally above, R¹⁰ is H or Z. In certain embodiments, R¹⁰ is H. In certain embodiments, R¹⁰ is Z.

[0210] As defined generally above, R¹¹ is H or Z. In certain embodiments, R¹¹ is H. In certain embodiments, R¹¹ is Z.

[0211] In certain embodiments, R¹⁰ and R¹¹ are H. In certain embodiments, R¹⁰ and R¹¹ are Z. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, and R¹¹ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ are H.

[0212] As defined generally above, R¹² is H or Z. In certain embodiments, R¹² is H. In certain embodiments, R¹² is Z.

[0213] As defined generally above, R¹³ is H or Z. In certain embodiments, R¹³ is H. In certain embodiments, R¹³ is Z.

[0214] In certain embodiments, R¹² and R¹³ are H. In certain embodiments, R¹² and R¹³ are Z. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹², and R¹³ are H. In certain embodiments, R¹, R², R³, R⁸, R⁹, R¹², and R¹³ are Z. In certain embodiments, R¹, R², R³, R¹², and R¹³ are Z. In certain embodiments, R⁸, R⁹, R¹², and R¹³ are Z.

[0215] As defined generally above, R¹⁴ is H or Z. In certain embodiments, R¹⁴ is H. In certain embodiments, R¹⁴ is Z.

[0216] As defined generally above, R¹⁵ is H or Z. In certain embodiments, R¹⁵ is H. In certain embodiments, R¹⁵ is Z.

[0217] As defined generally above, R¹⁶ is H or Z. In certain embodiments, R¹⁶ is H. In certain embodiments, R¹⁶ is Z.

[0218] As defined generally above, R¹⁷ is H or Z. In certain embodiments, R¹⁷ is H. In certain embodiments, R¹⁷ is Z.

[0219] In certain embodiments, R¹⁴, R¹⁵, R¹⁶, and R¹⁷ are H. In certain embodiments, R⁴, R⁵, R⁶, R⁷, R¹⁰, R¹¹, R¹⁴, R¹⁵, R¹⁶, and R¹⁷ are H.

[0220] As defined generally above, R¹⁸ is H or Z. In certain embodiments, R¹⁸ is H. In certain embodiments, R¹⁸ is Z. In certain embodiments, R¹⁸ is selected from the groups depicted in the compounds in Table 1, below.

[0221] As defined generally above, R¹⁹ is H or Z. In certain embodiments, R¹⁹ is H. In certain embodiments, R¹⁹ is Z.

[0222] In certain embodiments, R^{18} and R^{19} are H. In certain embodiments, R^{12} , R^{13} , R^{18} , and R^{19} are H. In certain embodiments, R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , and R^{19} are H. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , and R^{19} are H.

[0223] In certain embodiments, R^{18} and R^{19} are Z. In certain embodiments, R^{12} , R^{13} , R^{18} , and R^{19} are Z. In certain embodiments, R^1 , R^2 , R^3 , R^{12} , R^{13} , R^{18} , and R^{19} are Z. In certain embodiments, R^8 , R^9 , R^{12} , R^{13} , R^{18} , and R^{19} are Z. In certain embodiments, R^1 , R^2 , R^3 , R^8 , R^9 , R^{12} , R^{13} , R^{18} , and R^{19} are Z.

[0224] As defined generally above, R^{20} is H or Z. In certain embodiments, R^{20} is H. In certain embodiments, R^{20} is Z.

[0225] In certain embodiments, R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} are H. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^{10} , R^{11} , R^{14} , R^{15} , R^{16} , R^{17} , and R^{20} are H. In certain embodiments, R^4 , R^5 , R^6 , R^7 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} are H.

[0226] In certain embodiments, R^{12} , R^{13} , R^{18} , R^{19} , and R^{20} are Z. In certain embodiments, R^1 , R^2 , R^3 , and R^{20} are Z. In certain embodiments, R^8 , R^9 , and R^{20} are Z. In certain embodiments, R^1 , R^2 , R^3 , R^{12} , R^{13} , R^{18} , R^{19} , and R^{20} are Z. In certain embodiments, R^8 , R^9 , R^{12} , R^{13} , R^{18} , R^{19} , and R^{20} are Z. In certain embodiments, R^1 , R^2 , R^3 , R^8 , R^9 , R^{12} , R^{13} , R^{18} , R^{19} , and R^{20} are Z.

[0227] As defined generally above, Z is hydrogen or deuterium, provided that the abundance of deuterium in Z is at least 75%. In certain embodiments, the abundance of deuterium in Z is at least 80%. In certain embodiments, the abundance of deuterium in Z is at least 85%. In certain embodiments, the abundance of deuterium in Z is at least 90%. In certain embodiments, the abundance of deuterium in Z is at least 95%. In certain embodiments, the abundance of deuterium in Z is at least 97%. In certain embodiments, the abundance of deuterium in Z is at least 99%. In certain embodiments, the abundance of deuterium in Z is about 100%.

[0228] In certain embodiments, at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} is Z. In certain embodiments, one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} is Z. In certain embodiments, at least two of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} are Z. In certain embodiments, two of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} are Z. In certain embodiments, at least three of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} are Z. In certain embodiments, three of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} are Z. In certain embodiments, four or five of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , and R^{20} are Z. In certain

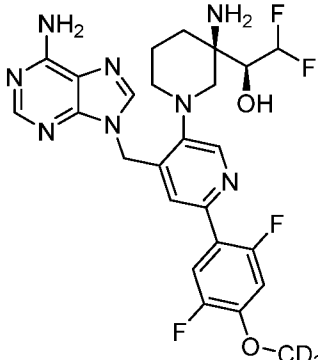
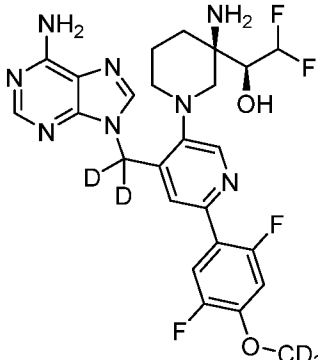
embodiments, more than five of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are Z.

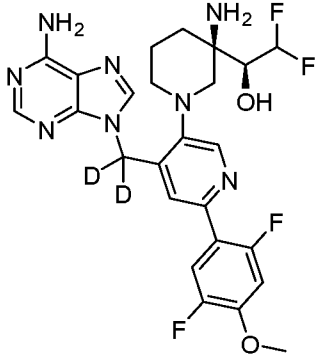
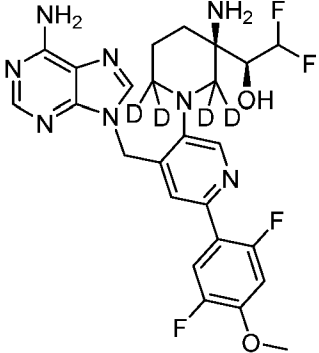
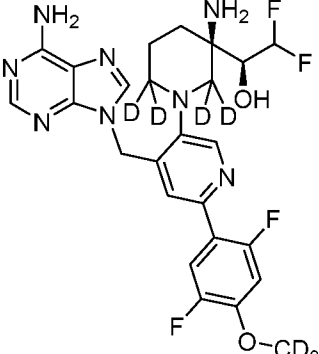
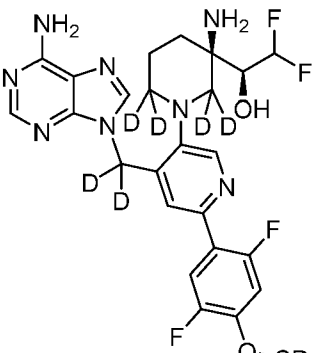
[0229] In certain embodiments, the compound has an enantiomeric excess of at least 85%. In certain embodiments, the compound has an enantiomeric excess of at least 90%. In certain embodiments, the compound has an enantiomeric excess of at least 95%. In certain embodiments, the compound has an enantiomeric excess of at least 98%.

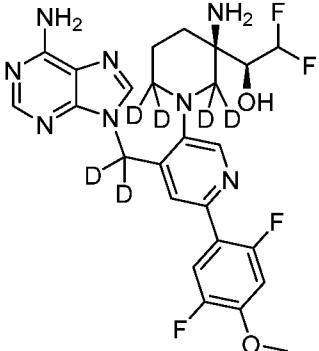
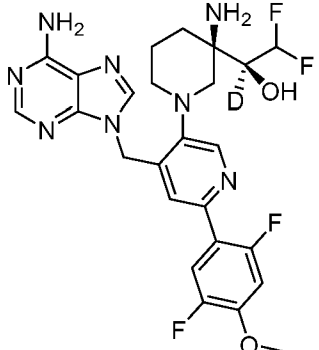
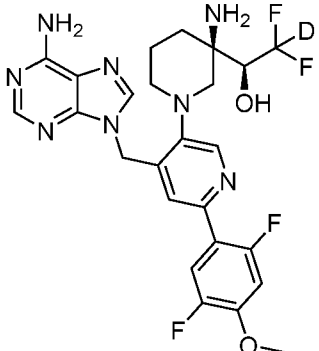
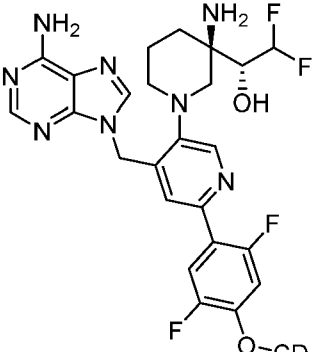
[0230] The description above describes multiple embodiments relating to compounds of Formula II-A. The patent application specifically contemplates all combinations of the embodiments.

[0231] Another aspect of the invention provides a compound in Table 1 or 2 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1 or 2 below. In certain embodiments, the compound is a compound in Table 1 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 1 below. In certain embodiments, the compound is a compound in Table 2 below, or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is a compound in Table 2 below.

TABLE 1.

Compound No.	Chemical Structure
I-1	
I-2	

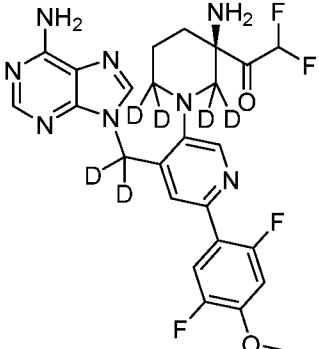
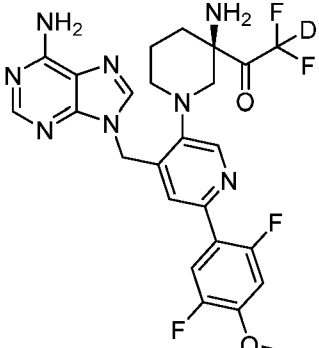
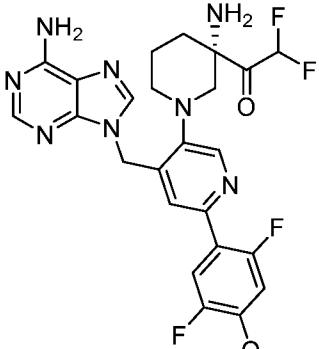
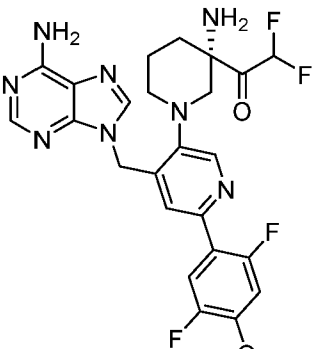
Compound No.	Chemical Structure
I-3	 <p>Chemical structure of compound I-3. It features a piperidine ring substituted with an amino group (NH₂) and a 2,2-difluoroethyl group. The piperidine nitrogen is connected to a pyridine ring. The pyridine ring is substituted with a 2,2-dideuterioethyl group and a 2,4-difluoro-3-methoxyphenyl group.</p>
I-4	 <p>Chemical structure of compound I-4. It features a piperidine ring substituted with an amino group (NH₂) and a 2,2-difluoroethyl group. The piperidine nitrogen is connected to a pyridine ring. The pyridine ring is substituted with a 2,2,3,3-tetradideuterioethyl group and a 2,4-difluoro-3-methoxyphenyl group.</p>
I-5	 <p>Chemical structure of compound I-5. It features a piperidine ring substituted with an amino group (NH₂) and a 2,2-difluoroethyl group. The piperidine nitrogen is connected to a pyridine ring. The pyridine ring is substituted with a 2,2,3,3-tetradideuterioethyl group and a 2,4-difluoro-3-(deuterio)methoxyphenyl group.</p>
I-6	 <p>Chemical structure of compound I-6. It features a piperidine ring substituted with an amino group (NH₂) and a 2,2-difluoroethyl group. The piperidine nitrogen is connected to a pyridine ring. The pyridine ring is substituted with a 2,2-dideuterioethyl group and a 2,4-difluoro-3-(deuterio)methoxyphenyl group.</p>

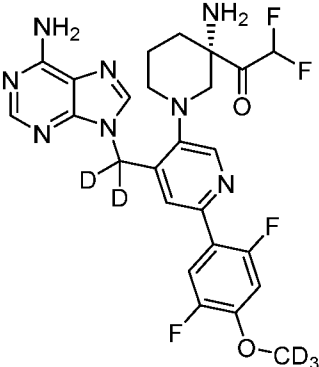
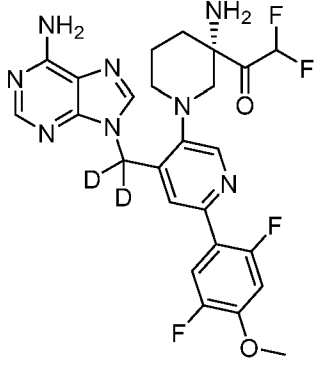
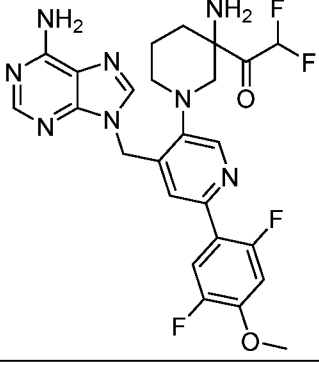
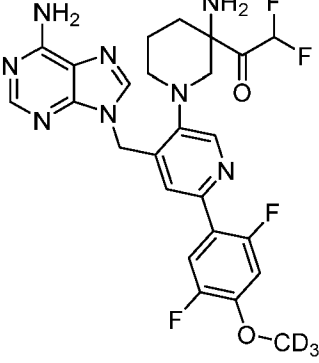
Compound No.	Chemical Structure
I-7	 <p>Chemical structure of compound I-7: A piperidine ring substituted with an amino group (NH₂) and a 2,4-difluoro-3-methoxyphenyl group. The piperidine ring is further substituted with a 2-amino-4,5,6-trideuterio-1H-benzotriazol-5-ylmethyl group and a 2,4-difluoro-3-methoxyphenyl group. The piperidine ring also has a hydroxyl group (OH) and a 2,2-difluoroethyl group attached to the 2-position.</p>
I-8	 <p>Chemical structure of compound I-8: A piperidine ring substituted with an amino group (NH₂) and a 2,4-difluoro-3-methoxyphenyl group. The piperidine ring is further substituted with a 2-amino-4,5,6-trideuterio-1H-benzotriazol-5-ylmethyl group and a 2,4-difluoro-3-methoxyphenyl group. The piperidine ring also has a hydroxyl group (OH) and a 2,2-difluoroethyl group attached to the 2-position.</p>
I-9	 <p>Chemical structure of compound I-9: A piperidine ring substituted with an amino group (NH₂) and a 2,4-difluoro-3-methoxyphenyl group. The piperidine ring is further substituted with a 2-amino-4,5,6-trideuterio-1H-benzotriazol-5-ylmethyl group and a 2,4-difluoro-3-methoxyphenyl group. The piperidine ring also has a hydroxyl group (OH) and a 2,2-difluoroethyl group attached to the 2-position.</p>
I-10	 <p>Chemical structure of compound I-10: A piperidine ring substituted with an amino group (NH₂) and a 2,4-difluoro-3-methoxyphenyl group. The piperidine ring is further substituted with a 2-amino-4,5,6-trideuterio-1H-benzotriazol-5-ylmethyl group and a 2,4-difluoro-3-methoxyphenyl group. The piperidine ring also has a hydroxyl group (OH) and a 2,2-difluoroethyl group attached to the 2-position.</p>

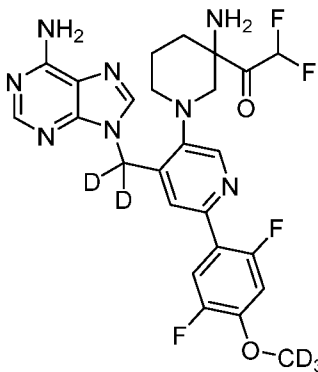
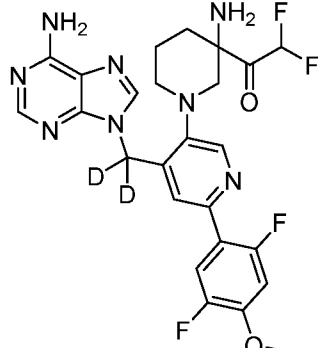
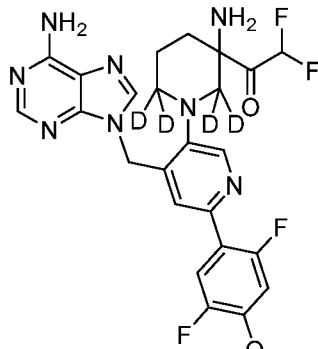
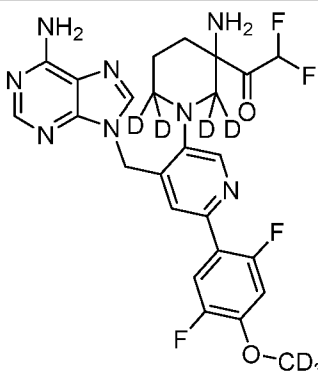
Compound No.	Chemical Structure
I-15	

TABLE 2.

Compound No.	Chemical Structure
II-1	
II-2	
II-3	

Compound No.	Chemical Structure
II-8	 <p>Chemical structure of compound II-8. It features a piperidine ring substituted with an amino group (NH₂) and a 2,2,2-trifluoroethyl group. The piperidine ring is connected via a methylene bridge to a pyridine ring. The pyridine ring is further substituted with a 2,4-difluoro-3-methoxyphenyl group and a 1,3-dideuterioethyl group.</p>
II-9	 <p>Chemical structure of compound II-9. It features a piperidine ring substituted with an amino group (NH₂) and a 2,2,2-trifluoroethyl group. The piperidine ring is connected via a methylene bridge to a pyridine ring. The pyridine ring is further substituted with a 2,4-difluoro-3-methoxyphenyl group and a 1,3-dideuterioethyl group.</p>
II-10	 <p>Chemical structure of compound II-10. It features a piperidine ring substituted with an amino group (NH₂) and a 2,2,2-trifluoroethyl group. The piperidine ring is connected via a methylene bridge to a pyridine ring. The pyridine ring is further substituted with a 2,4-difluoro-3-methoxyphenyl group and a 1,3-dideuterioethyl group.</p>
II-11	 <p>Chemical structure of compound II-11. It features a piperidine ring substituted with an amino group (NH₂) and a 2,2,2-trifluoroethyl group. The piperidine ring is connected via a methylene bridge to a pyridine ring. The pyridine ring is further substituted with a 2,4-difluoro-3-(methoxy-d₃)phenyl group and a 1,3-dideuterioethyl group.</p>

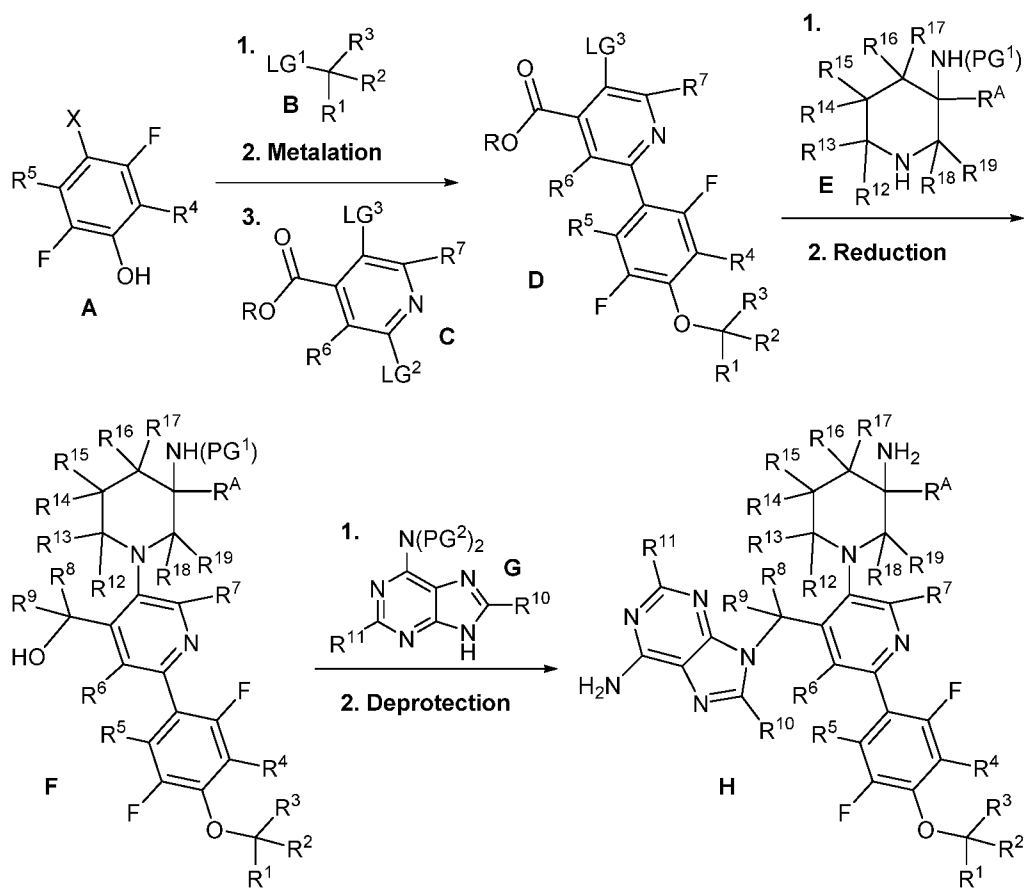
Compound No.	Chemical Structure
II-12	 <p>Chemical structure of compound II-12: A piperidine ring substituted with an amino group (NH₂) and a (1,1-difluoroethyl)amino group (NH₂CF₂CH₃). The piperidine nitrogen is connected to a pyridine ring. The pyridine ring is substituted with a 1,2-dideuterioethyl group (CD₂CH₂CD₃) and a 2,4-difluoro-3-methoxyphenyl group (F, F, O-CD₃).</p>
II-13	 <p>Chemical structure of compound II-13: A piperidine ring substituted with an amino group (NH₂) and a (1,1-difluoroethyl)amino group (NH₂CF₂CH₃). The piperidine nitrogen is connected to a pyridine ring. The pyridine ring is substituted with a 1,2-dideuterioethyl group (CD₂CH₂CD₃) and a 2,4-difluoro-3-methoxyphenyl group (F, F, O-CH₃).</p>
II-14	 <p>Chemical structure of compound II-14: A piperidine ring substituted with an amino group (NH₂) and a (1,1-difluoroethyl)amino group (NH₂CF₂CH₃). The piperidine nitrogen is connected to a pyridine ring. The pyridine ring is substituted with a methylene group (-CH₂-) and a 2,4-difluoro-3-methoxyphenyl group (F, F, O-CH₃).</p>
II-15	 <p>Chemical structure of compound II-15: A piperidine ring substituted with an amino group (NH₂) and a (1,1-difluoroethyl)amino group (NH₂CF₂CH₃). The piperidine nitrogen is connected to a pyridine ring. The pyridine ring is substituted with a methylene group (-CH₂-) and a 2,4-difluoro-3-(deuterio)methoxyphenyl group (F, F, O-CD₃).</p>

Compound No.	Chemical Structure
II-16	 <p>Chemical structure of compound II-16. It features a central pyridine ring substituted at the 2-position with a 2-amino-1H-imidazo[4,5-b]pyridin-4-ylidene group, at the 3-position with a dimethyl-d2-ethyl group, and at the 5-position with a 2-amino-2-(difluoroacetyl)pyrrolidine group. The pyridine ring is also substituted at the 4-position with a 2,4-difluoro-3-(methoxy-d3)phenyl group.</p>
II-17	 <p>Chemical structure of compound II-17. It features a central pyridine ring substituted at the 2-position with a 2-amino-1H-imidazo[4,5-b]pyridin-4-ylidene group, at the 3-position with a dimethyl-d2-ethyl group, and at the 5-position with a 2-amino-2-(difluoroacetyl)pyrrolidine group. The pyridine ring is also substituted at the 4-position with a 2,4-difluoro-3-methoxyphenyl group.</p>
II-18	 <p>Chemical structure of compound II-18. It features a central pyridine ring substituted at the 2-position with a 2-amino-1H-imidazo[4,5-b]pyridin-4-ylidene group, at the 3-position with a dimethyl-d2-ethyl group, and at the 5-position with a 2-amino-2-(difluoroacetyl)pyrrolidine group. The pyridine ring is also substituted at the 4-position with a 2,4-difluoro-3-methoxyphenyl group. The imidazo[4,5-b]pyridin-4-ylidene group is fully deuterated (d6).</p>
II-19	 <p>Chemical structure of compound II-19. It features a central pyridine ring substituted at the 2-position with a 2-amino-1H-imidazo[4,5-b]pyridin-4-ylidene group, at the 3-position with a dimethyl-d2-ethyl group, and at the 5-position with a 2-amino-2-(difluoroacetyl)pyrrolidine group. The pyridine ring is also substituted at the 4-position with a 2,4-difluoro-3-(methoxy-d3)phenyl group. The imidazo[4,5-b]pyridin-4-ylidene group is fully deuterated (d6).</p>

use of protecting groups or alternative reactions). Protecting group chemistry and strategy is well known in the art, for example, as described in detail in “Protecting Groups in Organic Synthesis”, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entire contents of which are hereby incorporated by reference.

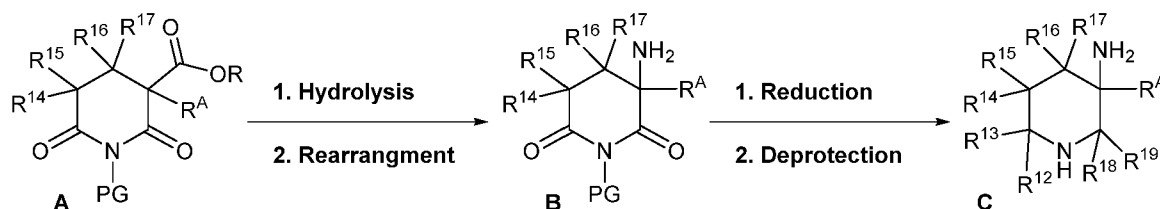
[0234] The synthetic route illustrated in Scheme 1 is a general method for preparing deuterium-enriched piperidinyl-methyl-purine amines and related compounds **H**. Subjecting halophenol **A** (wherein X is a halogen, such as Br or I) to methylation conditions (using, for example, a base, such as K₂CO₃ or DIPEA, and methylating agent **B** [such as commercially available iodomethane or perdeuterated iodomethane, wherein LG¹ is a leaving group, such as iodide]), followed by metalation of the halide X (using, for example, lithium/halogen exchange, optionally followed by conversion to, for example, an organozinc, boronate ester, or boronic acid [using, for example, a trialkyl boronate, and hydrolysis of the resulting boronate ester]), followed by transition-metal-mediated coupling with pyridine **C** (wherein LG² is a leaving group, such as bromide, iodide, or a sulfonate; LG³ is a leaving group, such as fluoride, chloride, or a sulfonate; and R is an appropriate group, such as methyl, ethyl, or benzyl) affords arylated pyridine ester **D**. Condensation of piperidine **E** (wherein R^A is -C(OH)(R²¹)-C(R²⁰)F₂ or -C(O)-C(R²⁰)F₂, and PG¹ is a protecting group, such as benzyl) with pyridine **D** (using, for example, nucleophilic aromatic substitution conditions with a base, such as K₂CO₃ or DIPEA, in a polar aprotic solvent, such as DMSO), followed by reduction of the ester group (using, for example, a metal hydride, such as LiAlH₄, or a metal deuteride, such as commercially available LiAlD₄), affords hydroxymethyl pyridine **F**. Activation of the hydroxyl group of pyridine **F**, either in a discrete step (for example, to a sulfonate, using, for example, tosyl chloride and a base, such as DIPEA) or *in situ* (for example, under Mitsunobu conditions), and displacement with protected adenine **G** (wherein PG² is a protecting group, such as Boc), followed by global deprotection (using, for example, reduction, such as hydrogenolysis, when at least one of PG¹ and/or PG² is benzyl, and/or acidic conditions, such as TFA or HCl, when at least one of PG¹ and/or PG² is Boc), affords deuterium-enriched piperidinyl-methyl-purine amines and related compounds **H**.

SCHEME 1.



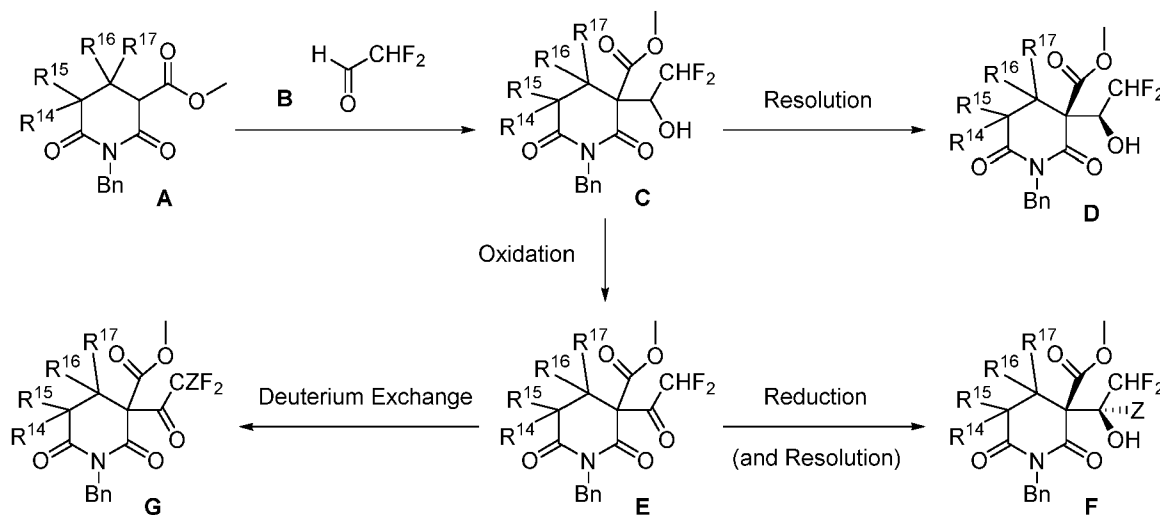
[0235] Deuterium-enrichment can also be included in piperidine intermediate E of Scheme 1, for example, as illustrated in Scheme 2. Subjecting piperidin-2,6-dione A (wherein PG is a protecting group, such as benzyl) to hydrolysis conditions (using, for example, LiOH and H₂O₂ in an alcoholic solvent, such as EtOH), followed by Lossen/Hofman/Curtius/Schmidt rearrangement affords aminopiperidine B. Reduction of the 2,6-dione (using, for example, a metal hydride, such as LiAlH₄ or NaBH₄, a metal deuteride, such as commercially available LiAlD₄ or NaBD₄, a borane, such as BH₃ or BD₃, or combinations thereof), followed by deprotection (using, for example, reduction, such as hydrogenolysis, when PG is benzyl) affords piperidine C, which may be deuterium-enriched. Several examples of deuterium incorporation in piperidine-2,6-diones are provided in, for example, US 2007/0276001 and Perrin, C. L., *et al.*, *J. Am. Chem. Soc.* (2005) vol. 127, no. 26, pp. 9641-9647.

SCHEME 2.



[0236] The synthetic route illustrated in Scheme 3 is a method for preparing specific piperidin-2,6-diones **A** of Scheme 2, including those where the R^A group may be deuterium-enriched. Aldol addition of piperidin-2,6-dione **A** to aldehyde **B** (or an equivalent thereof, such as an acetal or hemiacetal) affords alcohol **C**. Resolution of alcohol **C** (using, for example, chiral chromatography) affords the single stereoisomer **D**. Alternatively, oxidation of alcohol **C** affords ketone **E**. Reduction of ketone **E** (using, for example, a deuterium-enriched reducing agent, such as commercially available LiAlD_4), followed by resolution (using, for example, chiral chromatography) affords the single stereoisomer **F**. Alternatively, use of a deuterium-enriched stoichiometric reductant (for example, BD_3 or D_2) and a chiral catalyst (for example, an oxazaborolidine or a ruthenium/1,2-diphenylethane-1,2-diamine catalyst) affords single stereoisomer **F** without chiral chromatography. The enantiomers and diastereomers of alcohols **D** and **F** are prepared as single stereoisomers using analogous procedures. Finally, ketone **E** may alternatively be deuterated via its enol or enolate (using, for example, D_2O and an acid or base catalyst) to afford α -deutero ketone **G**.

SCHEME 3.



[0237] The modular synthetic routes illustrated in Schemes 1, 2, and 3 can also be readily modified by one of skill in the art to provide additional deuterium-enriched piperidinyl-methyl-

purine amines and related compounds by conducting functional group transformations, such as oxidations and reductions with deuterium-enriched reagents, on the intermediate and final compounds. Such functional group transformations are well known in the art, as described in, for example, "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992).

[0238] Compounds described herein can be provided in isolated or purified form. Isolated or purified compounds are a group of compounds that have been separated from their environment, such as from a crude reaction mixture if made in a laboratory setting, or removed from their natural environment if naturally occurring. Examples of the purity of the isolated compound include, for example, at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, to 100% by weight.

[0239] Another aspect of the invention provides a unit quantum of a deuterium-enriched compound described herein, such as an amount of at least (a) one μg of a disclosed deuterium-enriched compound, (b) one mg, or (c) one gram. In further embodiments, the quantum is, for example, at least 0.01, 0.02, 0.03, 0.04, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, or 1 mole of the compound. The present amounts also cover lab-scale (e.g., gram scale including 1, 2, 3, 4, 5 g, etc.), kilo-lab scale (e.g., kilogram scale including 1, 2, 3, 4, 5 kg, etc.), and industrial or commercial scale (e.g., multi-kilogram or above scale including 100, 200, 300, 400, 500 kg, etc.) quantities as these will be more useful in the actual manufacture of a pharmaceutical.

Industrial/commercial scale refers to the amount of product that would be produced in a batch that was designed for clinical testing, formulation, sale/distribution to the public, etc.

II. Therapeutic Applications of Deuterium-Enriched Piperidinyl-methyl-purine Amines and Related Compounds

[0240] The deuterium-enriched piperidinyl-methyl-purine amines and related compounds described herein, such as a compound of Formula I or II, or other compounds in Section I, provide therapeutic benefits to subjects suffering from cancer and other diseases or conditions. Accordingly, one aspect of the invention provides a method for treating a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2). The method comprises administering a therapeutically effective amount of a compound described herein, such as a compound of Formula I or II, to a subject in need thereof to treat the disease or condition. In certain embodiments, the compound is a compound of Formula I or II defined by one of the embodiments described above.

[0241] Examples of diseases or conditions that are mediated by NSD2 include but is not limited to breast cancer, cervical cancer, skin cancer (particularly skin squamous cell

carcinoma), ovarian cancer, gastric cancer, prostate cancer, pancreatic cancer, lung cancer, hepatocellular carcinoma, head and neck cancer, peripheral nerve sheath tumor, osteosarcoma, multiple myeloma, neuroblastoma, leukemia (particularly acute lymphoblastic leukemia), non-Hodgkin's lymphoma (particularly mantle cell lymphoma), and pulmonary arterial hypertension.

[0242] In certain embodiments, said disease or condition mediated by NSD2 is cancer.

[0243] In certain embodiments, said disease or condition mediated by NSD2 is selected from a solid tumor, leukemia, myeloma, lymphoma, and hypertension. In certain embodiments, said disease or condition mediated by NSD2 is a solid tumor. In certain embodiments, said disease or condition mediated by NSD2 is selected from leukemia, myeloma, and lymphoma. In certain embodiments, said disease or condition mediated by NSD2 is leukemia. In certain embodiments, said disease or condition mediated by NSD2 is myeloma. In certain embodiments, said disease or condition mediated by NSD2 is lymphoma. In certain embodiments, said disease or condition mediated by NSD2 is hypertension.

[0244] In certain embodiments, said disease or condition mediated by NSD2 is breast cancer, cervical cancer, skin cancer, ovarian cancer, gastric cancer, prostate cancer, pancreatic cancer, lung cancer, hepatocellular carcinoma, head and neck cancer, peripheral nerve sheath tumor, osteosarcoma, multiple myeloma, neuroblastoma, leukemia, non-Hodgkin's lymphoma, or pulmonary arterial hypertension. In certain embodiments, said disease or condition mediated by NSD2 is breast cancer. In certain embodiments, said disease or condition mediated by NSD2 is cervical cancer. In certain embodiments, said disease or condition mediated by NSD2 is ovarian cancer. In certain embodiments, said disease or condition mediated by NSD2 is gastric cancer. In certain embodiments, said disease or condition mediated by NSD2 is prostate cancer. In certain embodiments, said disease or condition mediated by NSD2 is pancreatic cancer. In certain embodiments, said disease or condition mediated by NSD2 is hepatocellular carcinoma. In certain embodiments, said disease or condition mediated by NSD2 is head and neck cancer. In certain embodiments, said disease or condition mediated by NSD2 is a peripheral nerve sheath tumor. In certain embodiments, said disease or condition mediated by NSD2 is osteosarcoma. In certain embodiments, said disease or condition mediated by NSD2 is multiple myeloma. In certain embodiments, said disease or condition mediated by NSD2 is neuroblastoma. In certain embodiments, said disease or condition mediated by NSD2 is pulmonary arterial hypertension.

[0245] In certain embodiments, said disease or condition mediated by NSD2 is acute lymphoblastic leukaemia, skin squamous cell carcinoma, or mantle cell lymphoma. In certain

embodiments, said disease or condition mediated by NSD2 is acute lymphoblastic leukaemia. In certain embodiments, said disease or condition mediated by NSD2 is skin squamous cell carcinoma. In certain embodiments, said disease or condition mediated by NSD2 is mantle cell lymphoma.

[0246] In certain embodiments, said disease or condition mediated by NSD2 is lung cancer. In certain embodiments, said disease or condition mediated by NSD2 is small cell or non-small cell lung cancer. In certain embodiments, said disease or condition mediated by NSD2 is small cell lung cancer. In certain embodiments, said disease or condition mediated by NSD2 is non-small cell lung cancer.

[0247] In certain embodiments, said disease or condition mediated by NSD2 is leukemia. In certain embodiments, said disease or condition mediated by NSD2 is acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), or chronic myelomonocytic leukemia (CMML). In certain embodiments, said disease or condition mediated by NSD2 is AML. In certain embodiments, said disease or condition mediated by NSD2 is CML. In certain embodiments, said disease or condition mediated by NSD2 is CMML.

[0248] In certain embodiments, said disease or condition mediated by NSD2 is skin cancer. In certain embodiments, said disease or condition mediated by NSD2 is melanoma, basal cell carcinoma, or squamous cell carcinoma. In certain embodiments, said disease or condition mediated by NSD2 is melanoma. In certain embodiments, said disease or condition mediated by NSD2 is basal cell carcinoma.

[0249] In certain embodiments, said disease or condition mediated by NSD2 is lymphoma. In certain embodiments, said disease or condition mediated by NSD2 is Hodgkin's lymphoma or non-Hodgkin's lymphoma. In certain embodiments, said disease or condition mediated by NSD2 is Hodgkin's lymphoma. In certain embodiments, said disease or condition mediated by NSD2 is non-Hodgkin's lymphoma. In certain embodiments, said disease or condition mediated by NSD2 is mantle cell lymphoma or diffuse large B cell lymphoma. In certain embodiments, said disease or condition mediated by NSD2 is diffuse large B cell lymphoma.

[0250] In certain embodiments, said disease or condition mediated by NSD2 is myeloma.

[0251] In certain embodiments, said disease or condition mediated by NSD2 is thyroid cancer. In certain embodiments, said disease or condition mediated by NSD2 is colon cancer.

[0252] In certain embodiments, the cancer overexpresses NSD2. In certain embodiments, the cancer has a mutation in NSD2. In certain embodiments, the cancer has an activating

mutation in NSD2. In certain embodiments, the cancer has the t(4;14)(p16.3;q32.3) translocation in NSD2. In certain embodiments, the cancer has an E1099K mutation in NSD2. In certain embodiments, the cancer has an T1150A mutation in NSD2.

[0253] 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 geriatric human.

[0254] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I or II, or other compounds in Section I) in the manufacture of a medicament. In certain embodiments, the medicament is for treating a disease or condition described herein, such as cancer.

[0255] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I or II, or other compounds in Section I) for treating a disease or condition, such as a disease or condition described herein (for example, cancer).

[0256] Further, compounds described herein, such as a compound of Formula I or II, or other compounds in Section I, inhibit the activity of nuclear SET domain-containing protein 2 (NSD2). Accordingly, another aspect of the invention provides a method of inhibiting the activity of nuclear SET domain-containing protein 2 (NSD2). The method comprises contacting a NSD2 with an effective amount of a deuterium-enriched piperidinyl-methyl-purine amine or related compound described herein, such as a compound of Formula I or II, or other compounds in Section I, to inhibit the activity of said NSD2. In certain embodiments, the compound is a compound of Formula I or II defined by one of the embodiments described above.

[0257] Compounds may be tested for ability to bind to and/or inhibit NSD2 activity according to any of various assays known in the art, including, for example, LC-MS/MS enzymatic assays monitoring SAH production, cellular FRET assays, cellular ELISA assays, methyltransferase enzymatic luminescence assays monitoring SAH production, and radiometric assays using tritium-labeled SAM. Such assays are described in, for example, WO 2021/028854 and Coussens, N. P. *et al. J. Biol. Chem.* (2018) Vol. 293, No. 35, pp. 13750-13755; the entirety of each of which is hereby incorporated by reference.

[0258] Benefits of deuterium-enriched compounds described herein can include increased metabolic stability. Such increased metabolic stability may result in a longer half-life for the deuterium-enriched compound in the patient's circulatory system and/or a higher C_{max} value in the patient's blood plasma. The longer half-life for the deuterium-enriched compound may

allow for less frequent administration of the deuterium-enriched compound to the patient while still achieving desirable levels of efficacy. A higher C_{max} value for the deuterium-enriched compound may provide greater efficacy in treating disease using the deuterium-enriched compound. Increased metabolic stability of the compound may also permit administering a lower dose of compound to patient – such lower dose of compound may reduce the frequency and/or magnitude of any adverse side effects.

[0259] Metabolic stability of a deuterium-enriched compound can be evaluated using procedures described in the literature for measuring the metabolic stability of compounds. For example, a test deuterium-enriched compound may be incubated at 37 °C in a solution containing hepatocytes obtained from a subject (e.g., a mouse, rat, dog, monkey, or human). An aliquot of the solution is obtained at several time points (e.g., 0, 15, 30, 60, 120, and 180 minutes), and the aliquot is evaluated by analytical methods (e.g., HPLC and/or HPLC-MS techniques) to determine the amount of original deuterium-enriched compound and/or the presence of any metabolites and/or degradation products of the original deuterium-enriched compound. A control article (e.g., verapamil) may be used as an internal standard during the experiment.

[0260] In a more specific embodiment, the metabolic stability of a deuterium-enriched compound can be evaluated by the following procedure: (i) prepare the appropriate substrate (e.g., nucleosomes) for the specific methyltransferase (e.g., NSD2) in freshly prepared reaction buffer, (ii) deliver the appropriate methyltransferase into the substrate solution and gently mix, (iii) deliver a deuterium-enriched test compound in DMSO into the methyltransferase reaction mixture by using, for example, acoustic technology (Echo 550, LabCyte Inc. Sunnyvale, CA) in the nanoliter range, incubate for 20 min at room temperature, (iv) deliver 1 μM of ³H-SAM (methyl donor) into the reaction mixture to initiate the reaction, (v) incubate the reaction mixture for 1 hour at 30°C, (vi) deliver the reaction mixture to filter-paper for detection, and (vii) analyze data using Excel and GraphPad Prism software.

III. Combination Therapy

[0261] Another aspect of the invention provides for combination therapy. Deuterium-enriched piperidiny-methyl-purine amine or related compounds described herein (e.g., a compound of Formula I or II, or other compounds in Section I) or their pharmaceutically acceptable salts may be used in combination with additional therapeutic agents to treat diseases or conditions, such as a cancer.

[0262] Accordingly, in some embodiments, the present invention provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein and co-administering simultaneously or sequentially an effective amount of one or more additional therapeutic agents, such as those described herein. In some embodiments, the method includes co-administering one additional therapeutic agent. In some embodiments, the method includes co-administering two additional therapeutic agents.

[0263] One or more other therapeutic agents may be administered separately from a compound or composition of the invention, as part of a multiple dosage regimen. Alternatively, one or more other therapeutic agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as a multiple dosage regime, one or more other therapeutic agent and a compound or composition of the invention may be administered simultaneously, sequentially or within a period of time from one another.

[0264] In certain embodiments, the additional therapeutic agent is an anti-cancer agent, anti-allergic agent, anti-nausea agent (or anti-emetic), pain reliever, cytoprotective agent, or a combination thereof. In certain embodiments, the additional therapeutic agent is an anti-cancer agent, an analgesic, an anti-inflammatory agent, or a combination thereof.

[0265] In certain embodiments, the additional therapeutic agent is an anti-cancer agent or chemo-therapeutic agent. Examples of anti-cancer agents considered for use in combination therapies of the invention include but are not limited erlotinib, bortezomib, fulvestrant, sunitib, imatinib mesylate, letrozole, finasunate, platins such as oxaliplatin, carboplatin, and cisplatin, finasunate, fluorouracil, rapamycin, leucovorin, lapatinib, lonafamib, sorafenib, gefitinib, camptothecin, topotecan, bryostatins, adezelesin, anthracyclin, carzelesin, bizelesin, dolastatin, auristatins, duocarmycin, eleutherobin, taxols such as paclitaxel or docetaxel, cyclophosphamide, doxorubicin, vincristine, prednisone or prednisolone, other alkylating agents such as mechlorethamine, chlorambucil, and ifosfamide, antimetabolites such as azathioprine or mercaptopurine, other microtubule inhibitors (vinca alkaloids like vincristine, vinblastine, vinorelbine, and vindesine, as well as taxanes), podophyllotoxins (etoposide, teniposide, etoposide phosphate, and epipodophyllotoxins), topoisomerase inhibitors, other cytotoxins such as actinomycin, daunorubicin, valrubicin, idarubicin, edrecolomab, epirubicin, bleomycin, plicamycin, mitomycin, as well as other anticancer antibodies (cetuximab, bevacizumab, ibrutinomab, abagovomab, adecatumumab, afutuzumab, alacizumab, alemtuzumab, anatumomab, apolizumab, bavituximab, belimumab, bivatumumab mertansine,

blinatumomab, brentuximab vedotin, cantuzumab mertansine, catumazomab, cetuximab, citatuzumab bogatox, cixutumumab, clivatuzumab tetraxetan, conatumumab, dacetuzumab, daclizumab, detumomab, ecromeximab, edrecolomab, elotuzumab, epratuzumab, ertumaxomab, etaracizumab, farletuzumab, figitumumab, fresolimumab, galiximab, gembatumumab vedotin, gemtuzumab, ibritumomab tiuxetan, inotuzumab ozogamicin, intetumumab, ipilimumab, iratumumab, labetuzumab, lexatumumab, lintuzumab, lucatumumab, lumilisimab, mapatumumab, matuzumab, milatuzumab, mitumomab, nacolomab tafenatox, naptumomab estafenatox, necitumumab, nimotuzumab, ofatumumab, olaratumab, oportuzumab monatox, oregovomab, panitumumab, pentumomab, pertuzumab, pintumomab, pritumumab, ramucirumab, rilotumumab, robatumumab, rituximab, sibrotuzumab, tacatuzumab tetraxetan, taplitumomab paptox, tenatumomab, ticilimumab, tigatuzumab, tositumomab or ¹³¹I-tositumomab, trastuzumab, tremelimumab, tuocotuzumab celmoleukin, veltuzumab, visilizumab, volocixumab, votumumab, zalutumumab, zanolimumab, IGN-101, MDX-010, ABX-EGR, EMD72000, ior-t1, MDX-220, MRA, H-11 scFv, huJ591, TriGem, TriAb, R3, MT-201, G-250, ACA-125, Onyvax-105, CD:-960, Cea-Vac, BrevaRex AR54, IMC-1C11, GlioMab-H, ING-1, anti-LCG MAbs, MT-103, KSB-303, Therex, KW2871, anti-HML.24, Anti-PTHrP, 2C4 antibody, SGN-30, TRAIL-RI MAb, Prostate Cancer antibody, H22xKi-r, ABX-Mai, Imuteran, Monopharm-C), and antibody-drug conjugates comprising any of the above agents (especially auristatins MMAE and MMAF, maytansinoids like DM-1, calicheamycins, or various cytotoxins).

[0266] In certain embodiments, the additional therapeutic agent is selected from anastrozole (ARIMIDEX®), bicalutamide (CASODEX®), bleomycin sulfate (BLENOXANE®), busulfan (MYLERAN®), busulfan injection (BUSULFEX®), capecitabine (XELODA®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (PARAPLATIN®), carmustine (BiCNU®), chlorambucil (LEUKERAN®), cisplatin (PLATINOL®), cladribine (LEUSTATIN®), cyclophosphamide (CYTOXAN® or NEOSAR®), cytarabine, cytosine arabinoside (CYTOSAR-U®), cytarabine liposome injection (DEPOCYT®), dacarbazine (DTIC-Dome®), dactinomycin (actinomycin D, COSMEGAN®), daunorubicin hydrochloride (CERUBIDINE®), daunorubicin citrate liposome injection (DAUNOXOME®), dexamethasone, docetaxel (TAXOTERE®), doxorubicin hydrochloride (ADRIAMYCIN®, RUBEX®), etoposide (VEPESID®), fludarabine phosphate (FLUDARA®), 5-fluorouracil (ADRUCIL®, EFUDEX®), flutamide (EULEXIN®), tezacitabine, gemcitabine (difluorodeoxycytidine), hydroxyurea (HYDREA®), idarubicin (IDAMYCIN®), ifosfamide (IFEX®), irinotecan (CAMPTOSAR®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (ALKERAN®), 6-mercaptopurine (PURINETHOL®), methotrexate (FOLEX®),

mitoxantrone (NOVANTRONE®), gemtuzumab ozogamicin (MYLOTARG™), paclitaxel (TAXOL®), nab-paclitaxel (ABRAXANE®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (GLIADEL®), tamoxifen citrate (NOLVADEX®), teniposide (VUMON®), 6-thioguanine, thiotepa, tirapazamine (TIRAZONE®), topotecan hydrochloride for injection (HYCAMPTIN®), vinblastine (VELBAN®), vincristine (ONCOVIN®), and vinorelbine (NAVELBINE®).

[0267] In certain embodiments, the additional therapeutic agent is capable of inhibiting BRAF, MEK, CDK4/6, SHP-2, HDAC, EGFR, MET, mTOR, PI3K or AKT, or a combination thereof. In a particular embodiment, the compounds of the present invention are combined with another therapeutic agent selected from vemurafinib, dabrafenib, LGX818, trametinib, MEK162, LEE011, PD-0332991, panobinostat, verinostat, romidepsin, cetuximab, gefitinib, erlotinib, lapatinib, panitumumab, vandetanib, INC280, everolimus, simolimus, BMK120, BYL719 or CLR457, or a combination thereof.

[0268] In certain embodiments, the additional therapeutic agent is selected based on the disease or condition that is being treated. For example, in the treatment of melanoma, the additional therapeutic agent is selected from aldesleukin (e.g., PROLEUKIN®), dabrafenib (e.g., TAFINLAR®), dacarbazine, recombinant interferon alfa-2b (e.g., INTRON® A), ipilimumab, trametinib (e.g., MEKINIST®), peginterferon alfa-2b (e.g., PEGINTRON®, SYLATRON™), vemurafinib (e.g., ZELBORAF®), and ipilimumab (e.g., YERVOY®).

[0269] For the treatment of ovarian cancer, the additional therapeutic agent is selected from doxorubicin hydrochloride (Adriamycin®), carboplatin (PARAPLATIN®), cyclophosphamide (CYTOXAN®, NEOSAR®), cisplatin (PLATINOL®, PLATINOL-AQ®), doxorubicin hydrochloride liposome (DOXIL®, DOX-SL®, EVACET®, LIPODOX®), gemcitabine hydrochloride (GEMZAR®), topotecan hydrochloride (HYCAMTIN®), and paclitaxel (TAXOL®).

[0270] For the treatment of thyroid cancer, the additional therapeutic agent is selected from doxorubicin hydrochloride (Adriamycin®), cabozantinib-S-malate (COMETRIQ®), and vandetanib (CAPRELSA®).

[0271] For the treatment of colon cancer, the additional therapeutic agent is selected from fluorouracil (e.g., ADRUCIL®, EFUDEX®, FLUOROPLEX®), bevacizumab (AVASTIN®), irinotecan hydrochloride (CAMPTOSTAR®), capecitabine (XELODA®), cetuximab (ERBITUX®), oxaliplatin (ELOXATIN®), leucovorin calcium (WELLCOVORIN®), regorafenib (STIVARGA®), panitumumab (VECTIBIX®), and ziv-aflibercept (ZALTRAP®).

[0272] For the treatment of lung cancer, the additional therapeutic agent is selected from methotrexate, methotrexate LPF (e.g., FOLEX®, FOLEX PFS®, Abitrexate®, MEXATE®, MEXATE-AQ®), paclitaxel (TAXOL®), paclitaxel albumin-stabilized nanoparticle formulation (ABRAXANE®), afatinib dimaleate (GILOTRIF®), pemetrexed disodium (ALIMTA®), bevacizumab (AVASTIN®), carboplatin (PARAPLATIN®), cisplatin (PLATINOL®, PLATINOL-AQ®), crizotinib (XALKORI®), erlotinib hydrochloride (TARCEVA®), gefitinib (IRESSA®), and gemcitabine hydrochloride (GEMZAR®).

[0273] For the treatment of pancreatic cancer, the other therapeutic agent may be selected from fluorouracil (ADRUCIL®), EFUDEX®, FLUOROPLEX®), erlotinib hydrochloride (TARCEVA®), gemcitabine hydrochloride (GEMZAR®), and mitomycin or mitomycin C (MITOZYTREXTM, MUTAMYCIN®).

[0274] For the treatment of cervical cancer, the additional therapeutic agent is selected from bleomycin (BLENOXANE®), cisplatin (PLATINOL®, PLATINOL-AQ®) and topotecan hydrochloride (HYCAMTIN®).

[0275] For the treatment of head and neck cancer, the additional therapeutic agent is selected from methotrexate, methotrexate LPF (e.g., FOLEX®, FOLEX PFS®, Abitrexate®, MEXATE®, MEXATE-AQ®), fluorouracil (ADRUCIL®, EFUDEX®, FLUOROPLEX®), bleomycin (BLENOXANE®), cetuximab (ERBITUX®), cisplatin (PLATINOL®, PLATINOL-AQ®) and docetaxel (TAXOTERE®).

[0276] For the treatment of leukemia, including chronic myelomonocytic leukemia (CMML), the additional therapeutic agent is selected from bosutinib (BOSULIF®), cyclophosphamide (CYTOXAN®, NEOSAR®), cytarabine (CYTOSAR-U®, TARABINE PFS®), dasatinib (SPRYCEL®), imatinib mesylate (GLEEVEC®), ponatinib (ICLUSIG®), nilotinib (TASIGNA®) and omacetaxine mepesuccinate (SYNRIBO®).

[0277] In some instances, patients may experience allergic reactions to the compounds of the present invention and/or other anti-cancer agent(s) during or after administration. Therefore, anti-allergic agents may be administered to minimize the risk of an allergic reaction. Suitable anti-allergic agents include corticosteroids, such as dexamethasone (e.g., DECADRON®), beclomethasone (e.g., BECLOVENT®), hydrocortisone (also known as cortisone, hydrocortisone sodium succinate, hydrocortisone sodium phosphate; e.g., ALA-CORT®, hydrocortisone phosphate, Solu-CORTEF®, HYDROCORT Acetate® and LANACORT®), prednisolone (e.g., DELTA-Cortel®, ORAPRED®, PEDIAPRED® and PRELONE®), prednisone (e.g., DELTASONE®, LIQUID RED®, METICORTEN® and

ORASONE®), methylprednisolone (also known as 6-methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate; e.g., DURALONE®, MEDRALONE®, MEDROL®, M-PREDNISOL® and SOLU-MEDROL®); antihistamines, such as diphenhydramine (e.g., BENADRYL®), hydroxyzine, and cyproheptadine; and bronchodilators, such as the beta-adrenergic receptor agonists, albuterol (e.g., PROVENTIL®), and terbutaline (BRETHINE®).

[0278] In other instances, patients may experience nausea during and after administration of the compound of the present invention and/or other anti-cancer agent(s). Therefore, anti-emetics may be administered in preventing nausea (upper stomach) and vomiting. Suitable anti-emetics include aprepitant (EMEND®), ondansetron (ZOFRAN®), granisetron HCl (KYTRIL®), lorazepam (ATIVAN®), dexamethasone (DECADRON®), prochlorperazine (COMPAZINE®), casopitant (REZONIC® and Zurrisa®), and combinations thereof.

[0279] In yet other instances, medication to alleviate the pain experienced during the treatment period is prescribed to make the patient more comfortable. Common over-the-counter analgesics, such as TYLENOL®, are often used. Opioid analgesic drugs such as hydrocodone/paracetamol or hydrocodone/acetaminophen (e.g., VICODIN®), morphine (e.g., ASTRAMORPH® or AVINZA®), oxycodone (e.g., OXYCONTIN® or PERCOCET®), oxymorphone hydrochloride (OPANA®), and fentanyl (e.g., DURAGESIC®) are also useful for moderate or severe pain.

[0280] Furthermore, cytoprotective agents (such as neuroprotectants, free-radical scavengers, cardioprotectors, anthracycline extravasation neutralizers, nutrients and the like) may be used as an adjunct therapy to protect normal cells from treatment toxicity and to limit organ toxicities. Suitable cytoprotective agents include amifostine (ETHYOL®), glutamine, dimesna (TAVOCEPT®), mesna (MESNEX®), dexrazoxane (ZINECARD® or TOTECT®), xaliproden (XAPRILA®), and leucovorin (also known as calcium leucovorin, citrovorum factor and folinic acid).

[0281] In yet another aspect, a compound of the present invention may be used in combination with known therapeutic processes, for example, with the administration of hormones or in radiation therapy. In certain instances, a compound of the present invention may be used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

[0282] The doses and dosage regimen of the active ingredients used in the combination therapy may be determined by an attending clinician. In certain embodiments, the compound

described herein (*e.g.*, a compound of Formula I or II, or other compounds in Section I) and the additional therapeutic agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating the disease or condition. In other embodiments, the compound described herein (*e.g.*, a compound of Formula I or II, or other compounds in Section I) and the additional therapeutic agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating the disease or condition. In certain embodiments, the compound described herein (*e.g.*, a compound of Formula I or II, or other compounds in Section I) and the additional therapeutic agent(s) are present in the same composition, which is suitable for oral administration.

[0283] In certain embodiments, the compound described herein (*e.g.*, a compound of Formula I or II, or other compounds in Section I) and the additional therapeutic agent(s) may act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of the therapy without reducing the efficacy of the therapy.

[0284] Another aspect of this invention is a kit comprising a therapeutically effective amount of a compound described herein (*e.g.*, a compound of Formula I or II, or other compounds in Section I), a pharmaceutically acceptable carrier, vehicle or diluent, and optionally at least one additional therapeutic agent listed above. In certain embodiments, the kit further comprises instructions, such as instructions for treating a disease described herein.

IV. Pharmaceutical Compositions and Dosing Considerations

[0285] 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 or II) and a pharmaceutically acceptable carrier.

[0286] 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.

[0287] 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.

[0288] 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.

[0289] 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.

[0290] 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.

[0291] 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.

[0292] 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.

[0293] 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.

[0294] 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.

[0295] 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.

[0296] 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.

[0297] 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.

[0298] 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.

[0299] 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.

[0300] 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.

[0301] 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.

[0302] 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.

[0303] 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.

[0304] 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.

[0305] 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.

[0306] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[0307] 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.

[0308] 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.

[0309] 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.

[0310] 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.

[0311] Injectable depot forms are made by forming microcapsule 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.

[0312] 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.

[0313] 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.

[0314] 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.

[0315] 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.

[0316] 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.

[0317] 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.

[0318] 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.

[0319] 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.

[0320] 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.

[0321] 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.

[0322] 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.

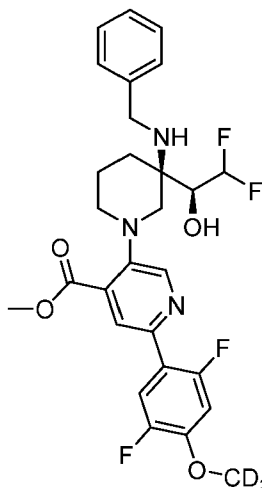
[0323] The invention further provides a unit dosage form (such as a tablet or capsule) comprising a deuterium-enriched piperidinyl-methyl-purine amine or related compound described herein in a therapeutically effective amount for the treatment of a disease or condition described herein.

EXAMPLES

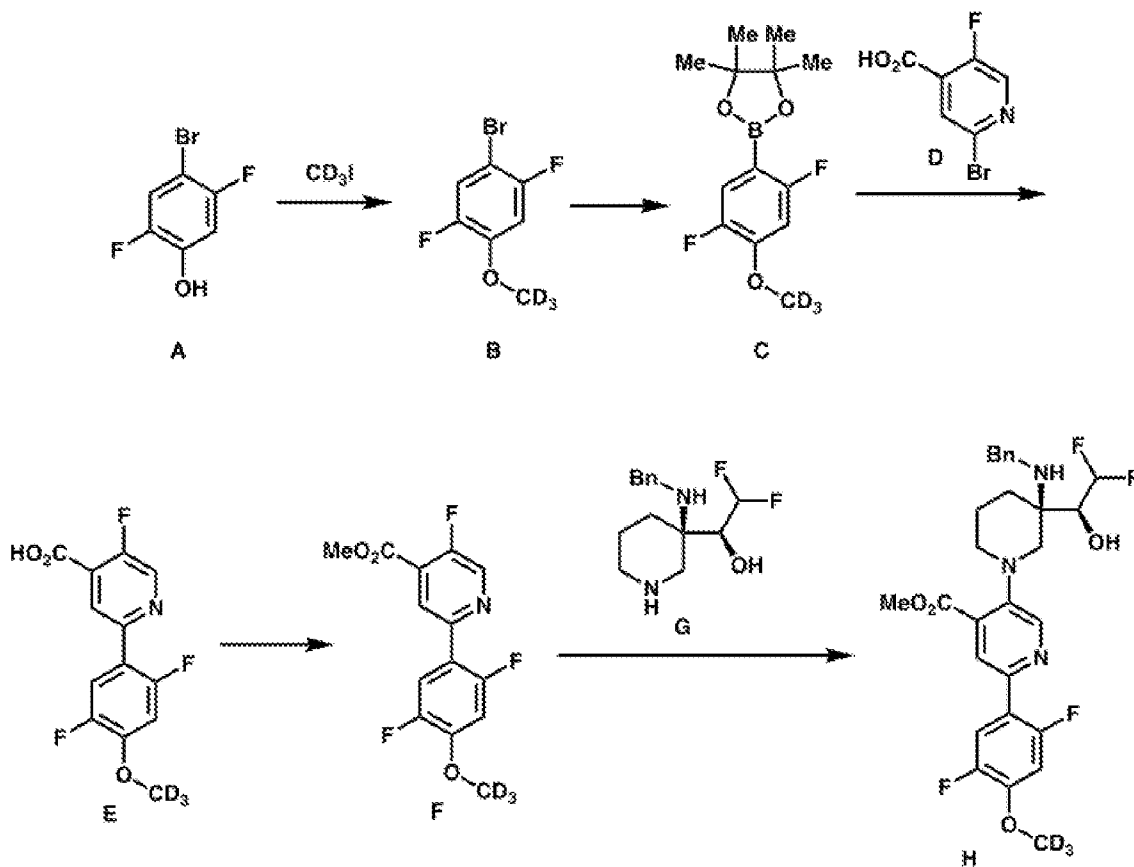
[0324] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustrating

certain aspects and embodiments of the present invention, and are not intended to limit the invention.

EXAMPLE 1 – Synthesis of methyl 5-((*R*)-3-(benzylamino)-3-((*S*)-2,2-difluoro-1-hydroxyethyl)piperidin-1-yl)-2-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)isonicotinate



[0325] The title compound was prepared using the following procedures.



[0326] Part 1: Preparation of Compound B

[0327] To a solution of compound **A** (200 g, 1.00 eq) and K_2CO_3 (330 g, 2.50 eq) in DMF (2.0 L) was added CD_3I (208 g, 1.50 eq) at 0 °C. The mixture was stirred at 20°C for 16 hrs. Then, the reaction mixture was quenched by the addition of H_2O (1.00 L), and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (500 mL x 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give compound **B** (190 g, crude) as a white solid. 1H NMR: ($CDCl_3$, 400MHz) δ 7.27 (dd, $J = 10.0, 6.4$ Hz, 1H), 6.78 (dd, $J = 9.6, 7.2$ Hz, 1H).

[0328] Part 2: Preparation of Compound C

[0329] To a solution of compound **B** (150 g, 1.00 eq) and BPD (337 g, 2.00 eq) in dioxane (1.05 L) was added AcOK (97.7 g, 1.50 eq) and $Pd(dppf)Cl_2$ (48.5 g, 0.10 eq) under an N_2 atmosphere. The resulting mixture was stirred at 90°C for 16 hrs. Then, the reaction mixture was cooled to 20°C and quenched by addition of H_2O (500 mL), and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (500 mL x 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give compound **C** (200 g, crude) as a white solid. 1H NMR: ($CDCl_3$, 400MHz) δ 7.38 (dd, $J = 11.2, 5.6$ Hz, 1H), 6.64 (dd, $J = 10.0, 6.8$ Hz, 1H), 1.26 (s, 12H).

[0330] Part 3: Preparation of Compound E

[0331] Compound **C** (200 g, 1.00 eq) and Compound **D** (136.8g, 0.85 eq) were mixed in dioxane (1.6 L) and water (400 mL). To the resulting mixture was added K_2CO_3 (202 g, 2.00 eq) and $Pd(dppf)Cl_2$ (53.6 g, 0.05 eq) under an N_2 atmosphere. Then, the mixture was stirred at 80°C for 16 hrs. Next, the reaction mixture was cooled to 20°C and quenched by addition of H_2O (500 mL), and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (500 mL x 2), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give compound **E** (390 g, crude) as a white solid. 1H NMR: (D_2O , 400 MHz) δ 8.45 (s, 1H), 7.75 (d, $J = 5.2$ Hz, 1H), 7.39 (dd, $J = 12.0, 7.2$ Hz, 1H), 6.98 (dd, $J = 12.4, 7.2$ Hz, 1H).

[0332] Part 4: Preparation of Compound F

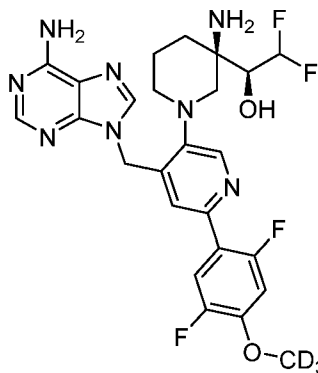
[0333] To a solution of compound **E** (390 g, 1.00 eq) in DMF (2.34 L) was added Me_2SO_4 (105.8 g, 0.70 eq). The resulting mixture was stirred at 25 °C for 16 hrs. Then, the reaction mixture was poured into H_2O (1.00 L) and filtered to remove the solids. The filtrate was concentrated under reduced pressure to give compound **F** (128 g, crude) as a white solid. 1H

NMR: (CDCl₃, 400 MHz) δ 8.65 (d, J = 2.0 Hz, 1H), 8.26 (d, J = 6.0 Hz, 1H), 7.81 (dd, J = 12.0, 7.2 Hz, 1H), 6.79 (dd, J = 12.4, 6.8 Hz, 1H), 4.01 (s, 3H). LCMS: ESI MS+1=301.0

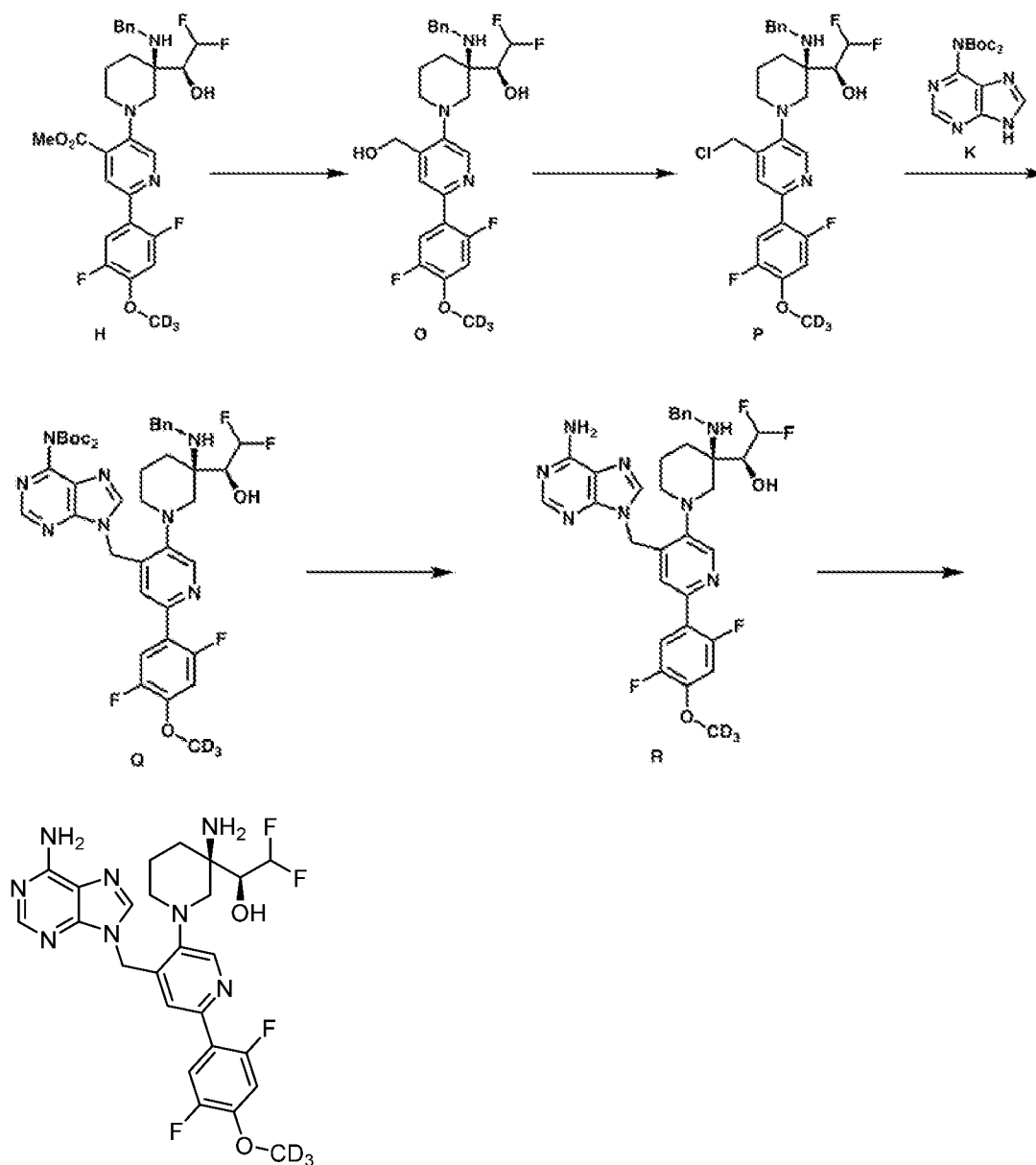
Part 5: Preparation of Compound H, which has the chemical name methyl 5-((*R*)-3-(benzylamino)-3-((*S*)-2,2-difluoro-1-hydroxyethyl)piperidin-1-yl)-2-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)isonicotinate

[0334] To a solution of compound **F** (50.0 g, 1.00 eq) in NMP (300 mL) was added DIEA (172 g, 8.00 eq) and compound **G** (102 g, 1.00 eq). The resulting mixture was stirred at 100 °C for 12 hrs. Then, the reaction mixture was cooled to 20 °C and quenched by addition of H₂O (500 mL), and extracted with EtOAc (100 mL x 2). To the combined organic layers were added H₂O (300 mL) and 35% HCl was added dropwise to adjust pH~1-2 at 20 °C providing a suspension. The suspension was filtered, and the resulting filter cake was dissolved by 2-MeTHF (500 mL). To the solution was added 20% mixed solvent of KHCO₃/H₂O (500 mL) and extracted by 2-MeTHF (200 mL x 3). The 2-MeTHF phase was washed with brine (500 mL x 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give compound **H** (85.0 g) as a yellow oil. ¹H NMR: (CDCl₃, 400MHz) δ 8.38 (s, 1H), 7.85 (s, 1H), 7.69(dd, J = 12.4, 7.6 Hz, 1H), 7.28-7.17 (m, 5H), 6.65 (dd, J = 12.0, 6.8 Hz, 1H), 5.92 (td, J = 55.2, 3.6 Hz, 1H), 3.71-3.55 (m, 6H), 3.20-3.17 (m, 2H), 2.96 (d, J = 11.6 Hz, 1H), 2.85-2.77 (m, 1H), 2.05-2.01 (m, 1H), 1.68-1.64 (m, 1H). LCMS: ESI MS+1=550.3.

EXAMPLE 2 – Synthesis of Compound I-1



[0335] The title compound was prepared using the following procedures.



I-1

[0336] Part 1: Preparation of Compound O

[0337] To a solution of compound **H** (33.0 g, 1.00 eq) in THF (297 mL) and MeOH (33.0 mL) was added LiBH₄ (2.00 M, 59.9 mL, 2.00 eq) at 20 °C, and then the reaction mixture was stirred at 40 °C for 3 hrs. Next, the reaction was quenched by the additional of water (100 mL), and the resulting mixture was extracted with EtOAc (50.0 mL x 3). The organic phase of the mixture was isolated and washed with brine (200 mL), dried with anhydrous Na₂SO₄, and concentrated under vacuum to provide compound **O** (29.0 g) as a white solid. ¹HNMR: (DMSO-d, 400MHz) δ 8.35 (s, 1H), 7.90 (s, 1H), 7.75-7.73 (m, 1H), 7.38-7.30 (m, 4H), 7.24-7.22 (m, 2H), 6.26 (t, *J* = 55.2 Hz, 1H), 5.72-7.71 (d, *J* = 6.4 Hz, 1H), 5.41 (t, *J* = 6.4 Hz, 1H),

4.59-4.57 (d, $J = 5.6$ Hz, 2H), 3.80-3.76 (m, 2H), 3.66-3.64 (m, 1H), 3.12 (d, $J = 11.6$ Hz, 1H), 2.93 (d, $J = 10.8$ Hz, 1H), 2.71-2.69 (m, 1H), 2.22-2.21 (m, 1H), 1.84-1.69 (m, 4H). LCMS: ESI MS+1=523.2.

[0338] Part 2: Preparation of Compound P

[0339] To a solution of compound **O** (28.0 g, 1.00 eq) in DCM (280 mL) was added SOCl_2 (10.96 g, 1.60 eq) in portions at 0 °C, then the reaction mixture was stirred at 0 °C for 2 hrs. H_2O (20.0 mL) was added to the reaction mixture, and the resulting mixture was stirred at 25 °C for 16 hrs. Next, the reaction mixture was slowly quenched by the addition of aq. Na_2CO_3 (100 mL, 10%). The resulting mixture was extracted with DCM (100 mL x 2). The combined organic layers were washed with brine (200 mL x 2), dried over Na_2SO_4 , and concentrated under vacuum to provide compound **P** (29.0 g) as a yellow solid. ^1H NMR: (CDCl_3 , 400MHz) δ 8.38 (s, 1H), 7.75 (s, 1H), 7.70 (dd, $J = 12.4, 7.6$ Hz, 2H), 7.28-7.18 (m, 5H), 6.67 (dd, $J = 12.4, 7.2$ Hz, 1H), 5.95 (td, $J = 55.2, 3.2$ Hz, 1H), 4.56 (d, $J = 12.0$ Hz, 1H), 4.49 (d, $J = 12.0$ Hz, 1H), 3.74-3.62 (m, 3H), 3.06-3.05 (m, 3H), 2.81-2.79 (m, 1H), 2.06-2.02 (m, 1H), 1.92 (s, 1H), 1.84-1.80 (m, 2H), 1.74-1.71 (m, 1H). LCMS: ESI MS+1=541.2

[0340] Part 3: Preparation of Compound Q

[0341] To a solution of compound **P** (29.0 g, 1.00 eq) and compound **K** (18.0 g, 1.30 eq) in DMA (174 mL) was added K_2CO_3 (14.8 g, 2.00 eq). The resulting mixture was stirred at 20 °C for 12 hrs. Then, the reaction mixture was quenched by addition of H_2O (200 mL) at 0 to 5 °C, then extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (200 mL x 4), dried over Na_2SO_4 , filtered, and concentrated under vacuum to provide a residue. The residue was purified by column chromatography to provide compound **Q** (19.8 g) as a yellow solid.

[0342] Part 4: Preparation of Compound R

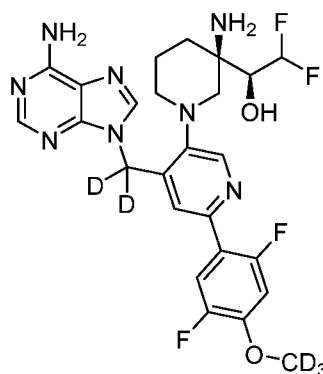
[0343] A solution of compound **Q** (19.8 g, 1.00 eq) in TFA (59.4 mL) and DCM (118 mL) was stirred at 40 °C for 16 hrs. Then, the reaction mixture was concentrated under reduced pressure to remove TFA and DCM. The resulting residue was diluted with MeOH (40.0 mL) and then poured into aq. Na_2CO_3 (50.0 mL). A solid was precipitated out of the mixture; the solid was collected by filtration. The filter cake was washed with MeOH and dried under vacuum to provide compound **R** (16.0 g, crude) as a white solid. ^1H NMR: (DMSO-d_6 , 400MHz) δ 8.84-8.79 (br s, 1H), 8.55 (s, 1H), 8.23 (s, 1H), 8.06 (s, 1H), 7.69 (dd, $J = 12.4, 7.6$ Hz, 1H), 7.54-7.53 (m, , 2H), 7.36-7.25 (m, 5H), 7.13 (dd, $J = 12.8, 7.6$ Hz, 1H), 7.00 (s, 1H), 6.46 (m, 1H),

5.81-5.74 (m, 1H), 5.57-5.53 (br d, $J = 16.0$ Hz, 2H), 4.42-4.30 (m, 3H), 3.50-3.45 (m, 2H), 3.00 (m, 2H), 2.82 (m, 1H), 2.05-1.90 (m, 4H), 1.75 (m, 1H). LCMS: ESI MS+1=640.4

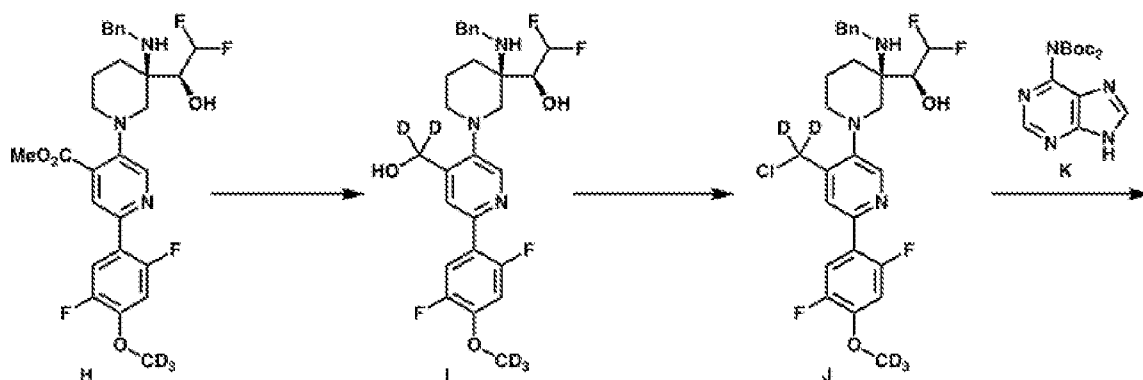
[0344] Part 5: Preparation of Compound I-1

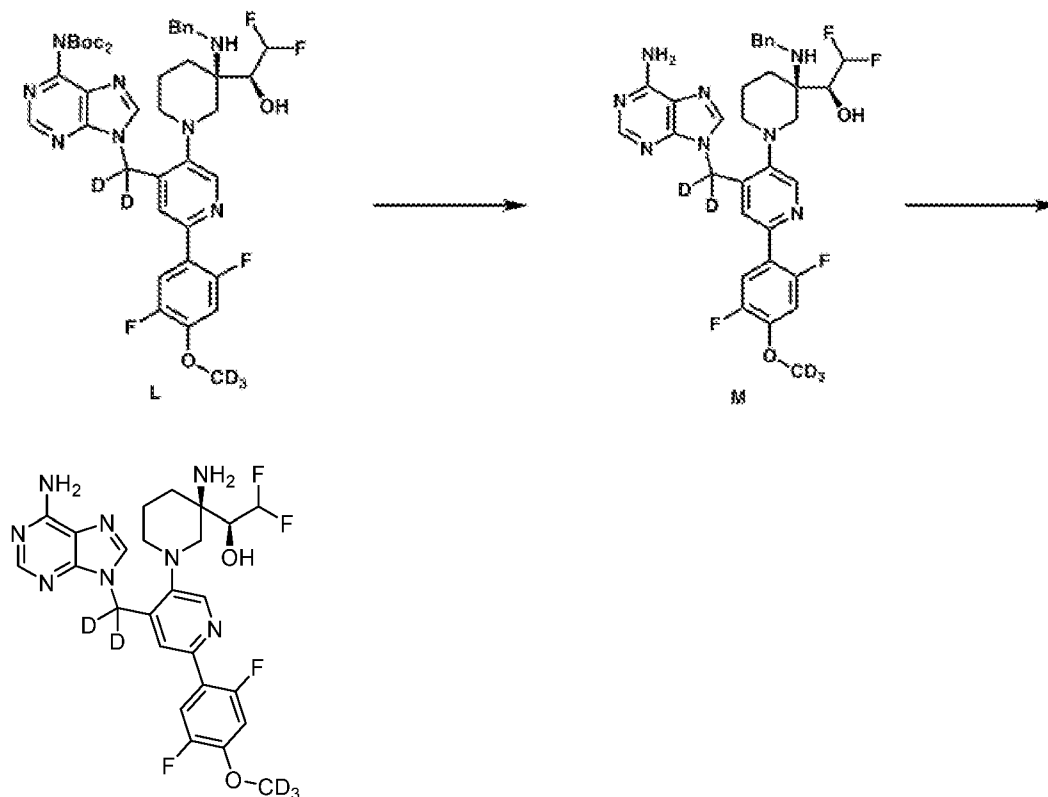
[0345] To a solution of compound **R** (14.00 g, 1.00 eq) in THF (70.0 mL) was added Pd(OH)₂ (1.40 g, 10%) and TFA (7.48 g, 3.00 eq) under N₂ atmosphere. The resulting suspension was degassed and purged with H₂ three times. The resulting mixture was stirred under H₂ (15 Psi) at 20 °C for 16 hrs. Next, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to provide a residue. The residue was purified by prep-HPLC to provide compound **I-1** (6.70 g) as an off-white solid. ¹H NMR: (DMSO-d, 400MHz) δ 8.49 (s, 1H), 8.26 (s, 1H), 8.11 (s, 1H), 7.71-7.66 (m, 1H), 7.29 (s, 1H), 7.13-7.08 (m, 1H), 6.92 (s, 1H), 6.18 (t, $J = 56.4$ Hz, 1H), 5.71 (d, $J = 4.8$ Hz, 1H), 5.56-5.43 (m, 2H), 3.78 (br s, 1H), 3.10 (d, $J = 10.8$ Hz, 2H), 3.08 (br s, 1H), 2.91 (br s, 1H), 2.77 (d, $J = 7.6$ Hz, 1H), 1.89-1.72 (m, 4H), 1.47 (s, 1H). MS (ES API+), 550.0, calc'd 550.2 (M+H+).

EXAMPLE 3 – Synthesis of Compound I-2



[0346] The title compound was prepared using the following procedures.





[0347] Part 1: Preparation of Compound I

[0348] To a solution of compound **H** (70.0 g, 1.00 eq) in THF (490 mL) was added LiAlD₄ (7.24 g, 1.50 eq) at 20–30 °C, and the reaction stirred at 40 °C for 3 hrs. Then, the reaction was quenched with D₂O (200 mL) and extracted with EtOAc (100 mL x 3). The organic phase was washed with brine (500 mL), dried with anhydrous Na₂SO₄ and concentrated under vacuum to provide compound **I** (63.0 g, crude) as a yellow solid. ¹HNMR: (CDCl₃, 400MHz δ 8.36 (s, 1H), 7.73 (s, 1H), 7.69 (dd, J = 14.8, 7.6 Hz, 1H), 7.28-7.19 (m, 6H), 6.67 (dd, J = 12.0, 6.8 Hz, 1H), 5.96 (td, J = 56.0, 4.0 Hz, 1H), 3.72-3.64 (m, 2H), 3.10-3.07 (m, 1H), 3.03-2.96 (m, 2H), 2.83-2.81 (m, 1H), 1.97-1.95 (m, 1H), 1.84-1.74(m, 3H). LCMS: ESI MS+1=525.2)

[0349] Part 2: Preparation of Compound J

[0350] To a solution of compound **I** (54.0 g, 1.00 eq) in DCM (540 mL) was added SOCl₂ (18.00 g, 1.50 eq) in portions at 0 °C. Then the reaction mixture was stirred at 0 °C for 2 hrs. Next, water (60.0 mL) was added to the reaction mixture, and the resulting mixture was stirred at 25 °C for 16 hrs. Then, the reaction mixture was slowly quenched with aq. Na₂CO₃ (200 mL, 10%) and extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (200 mL x 2), dried over Na₂SO₄, and concentrated under vacuum to provide

compound **J** (55.0 g, crude) as a yellow solid. ¹H NMR: (CDCl₃, 400MHz) δ 8.38 (s, 1H), 7.74 (s, 1H), 7.71 (dd, *J* = 14.4, 6.8 Hz, 1H), 7.28-7.18 (m, 5H), 6.68 (dd, *J* = 12.0, 6.8 Hz, 1H), 5.97 (td, *J* = 55.2, 3.2 Hz, 1H), 3.77-3.61 (m, 3H), 3.06-3.05 (m, 3H), 2.82-2.79 (m, 1H), 2.05-2.01 (m, 1H), 1.82-1.75 (m, 3H). LCMS: ESI MS+1=543.1

[0351] Part 3: Preparation of Compound L

[0352] To a solution of compound **J** (50.0 g, 1.00 eq) and compound **K** (40.0 g, 1.30 eq) in DMA (300 mL) was added K₂CO₃ (25.4 g, 2.00 eq). The resulting mixture was stirred at 20 °C for 12 hrs. Then, the reaction mixture was quenched by addition of D₂O (500 mL) and then extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (200 mL x 4), dried over Na₂SO₄, and filtered. The resulting residue was purified by column chromatography to provide compound **L** (60.0 g) as a yellow solid. ¹H NMR: (CDCl₃, 400MHz) δ 8.69 (s, 1H), 8.48 (s, 1H), 7.95 (s, 1H), 7.66 (dd, *J* = 12.4, 7.2 Hz, 1H), 7.29-7.15 (m, 6H), 6.55 (dd, *J* = 12.4, 7.2 Hz, 1H), 6.02 (t, *J* = 56.0 Hz, 1H), 3.80-3.71 (m, 2H), 3.31-3.30 (m, 1H), 3.00-2.88 (m, 3H), 1.85-1.78 (m, 4H), 1.36 (s, 18H).

[0353] Part 4: Preparation of Compound M

[0354] Compound **L** (30.0 g, 1.00 eq) was mixed with DCM (180 mL), and then TFA (90.0 mL) was added. The resulting mixture was stirred at 40 °C for 16 hrs. Then, the reaction mixture was concentrated under reduced pressure to remove TFA and DCM. The resulting residue was diluted with MeOD (100 mL) and then poured into aq. Na₂CO₃ (200 mL). Solid was precipitated which was collected by filtration. The filter cake was washed with MeOH and dried under vacuum to provide compound **M** (27.0 g, crude) as a white solid. ¹H NMR: (DMSO-d, 400MHz) δ 8.52 (s, 1H), 8.21 (s, 1H), 7.99 (s, 1H), 7.68 (dd, *J* = 12.4, 7.2 Hz, 1H), 7.40-7.11 (m, 8H), 6.96 (s, 1H), 6.28 (t, *J* = 54.8 Hz, 1H), 5.84 (br s, 1H), 4.01-3.95 (m, 2H), 3.86-3.72 (m, 1H), 3.06-3.02 (m, 2H), 2.85-2.83 (m, 1H), 2.44-2.43 (m, 1H), 1.75-1.73 (m, 4H). LCMS: ESI MS+1=642.4)

[0355] Part 5: Preparation of Compound I-2

[0356] To a solution of compound **M** (27.0 g crude, 1.00 eq) in THF (135 mL) was added Pd(OH)₂ (6.00 g, 10.0%) and TFA (14.4 g, 3.00 eq) under N₂ atmosphere. The suspension was degassed and purged with H₂ three times. The mixture was stirred under H₂ (15 Psi) at 20 °C for 16 hrs. Then, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to provide a residue. The residue was dissolved by EtOH (40.0 mL) and then a solution of a loweralkyl dicarboxylic acid in D₂O (7.50 mL) was added dropwise. The mixture was stirred at 50 °C for 16 hrs. Next, the mixture was filtered, and the filter cake was

concentrated. The filter cake was neutralized using Na₂CO₃ (50.0 mL) and then filtered to provide compound **I-2** as a white solid. ¹H NMR: (DMSO-d, 400MHz) δ 8.50 (s, 1H), 8.26 (s, 1H), 8.13 (s, 1H), 7.71-7.66 (m, 1H), 7.32 (s, 1H), 7.14-7.09 (m, 1H), 6.98 (s, 1H), 6.21 (td, J = 55.6, 3.6 Hz, 1H), 3.88-3.81 (m, 2H), 3.12 (d, J = 12.0 Hz, 1H), 3.04-3.02 (m, 1H), 2.93-2.85 (m, 2H), 1.89-1.72 (m, 3H), 1.58-1.56 (m, 1H). MS (TOF ES+), 552.2495. 552.2507 calc'd (M+H+).

INCORPORATION BY REFERENCE

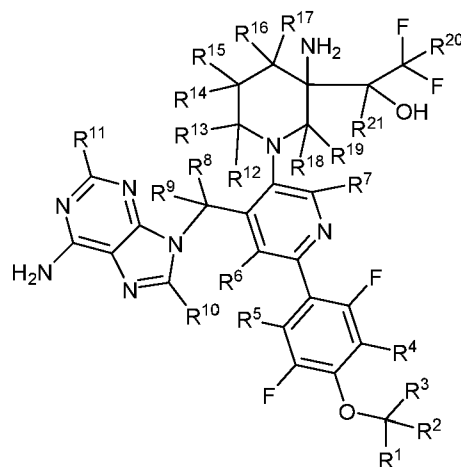
[0357] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0358] 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 compound represented by Formula I:



(I)

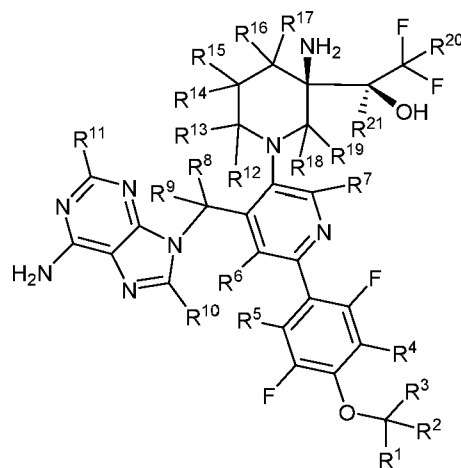
or a pharmaceutically acceptable salt thereof; wherein:

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%;

provided that at least one of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ is Z.

2. The compound of claim 1, wherein the compound is a compound of Formula I.
3. The compound of claim 1, wherein the compound is represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof; wherein:

R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²¹ are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%;

or a pharmaceutically acceptable salt thereof; wherein:

$R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}$, and R^{20} are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%.

10. The compound of claim 9, wherein the compound is a compound of Formula II-A.
11. The compound of any one of claims 7-10, wherein at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}$, and R^{20} is Z.
12. The compound of any one of claims 1-11, wherein R^1, R^2 , and R^3 are Z.
13. The compound of any one of claims 1-11, wherein R^1, R^2 , and R^3 are H.
14. The compound of any one of claims 1-13, wherein R^4, R^5, R^6 , and R^7 are H.
15. The compound of any one of claims 1-14, wherein R^8 and R^9 are Z.
16. The compound of any one of claims 1-14, wherein R^8 and R^9 are H.
17. The compound of any one of claims 1-16, wherein R^{10} and R^{11} are H.
18. The compound of any one of claims 1-17, wherein R^{12} and R^{13} are Z.
19. The compound of any one of claims 1-17, wherein R^{12} and R^{13} are H.
20. The compound of any one of claims 1-19, wherein R^{14}, R^{15}, R^{16} , and R^{17} are H.
21. The compound of any one of claims 1-20, wherein R^{18} and R^{19} are Z.
22. The compound of any one of claims 1-20, wherein R^{18} and R^{19} are H.
23. The compound of any one of claims 1-22, wherein R^{20} is Z.
24. The compound of any one of claims 1-22, wherein R^{20} is H.
25. The compound of any one of claims 1-24, wherein the abundance of deuterium in Z is at least 90%.
26. The compound of any one of claims 1-24, wherein the abundance of deuterium in Z is at least 95%.
27. The compound of any one of claims 1-26, wherein the compound has an enantiomeric excess of at least 85%.
28. The compound of any one of claims 1-26, wherein the compound has an enantiomeric excess of at least 90%.

29. The compound of any one of claims 1-26, wherein the compound has an enantiomeric excess of at least 95%.
30. A compound in Table 1 or 2 herein, or a pharmaceutically acceptable salt thereof.
31. A pharmaceutical composition comprising a compound of any one of claims 1-30 and a pharmaceutically acceptable carrier.
32. A method for treating a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2), comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-30 to treat the disease or condition.
33. The method of claim 32, wherein said disease or condition mediated by NSD2 is cancer.
34. The method of claim 32, wherein said disease or condition mediated by NSD2 is selected from a solid tumor, leukemia, myeloma, lymphoma, and hypertension.
35. The method of claim 32, wherein said disease or condition mediated by NSD2 is breast cancer, cervical cancer, skin cancer, ovarian cancer, gastric cancer, prostate cancer, pancreatic cancer, lung cancer, hepatocellular carcinoma, head and neck cancer, peripheral nerve sheath tumor, osteosarcoma, multiple myeloma, neuroblastoma, leukemia, non-Hodgkin's lymphoma, or pulmonary arterial hypertension.
36. The method of claim 32, wherein said disease or condition mediated by NSD2 is acute lymphoblastic leukaemia, skin squamous cell carcinoma, or mantle cell lymphoma.
37. The method of any one of claims 32-36, wherein the subject is a human.
38. A method of inhibiting the activity of nuclear SET domain-containing protein 2 (NSD2), comprising contacting a NSD2 with an effective amount of a compound of any one of claims 1-30 to inhibit the activity of said NSD2.