

**DEUTERIUM-ENRICHED PIPERIDINYL-METHYL-PURINE AMINE SALTS,
CRYSTALLINE FORMS, AND THEIR USE IN TREATING MEDICAL
DISEASES AND CONDITIONS**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/600,374, filed on November 17, 2023, the entirety of which is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention provides deuterium-enriched piperidiny-methyl-purine amine salts, crystalline forms, pharmaceutical compositions, their use in inhibiting NSD2, and their use in the treatment of a disease or condition, such as cancer.

BACKGROUND

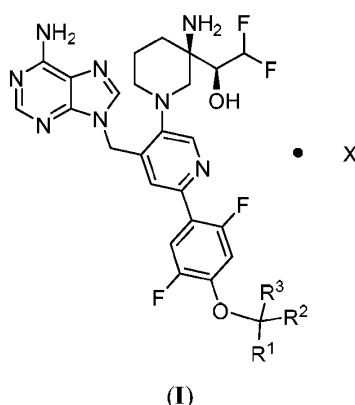
[0003] Cancer continues to be a significant health problem despite the substantial research efforts and scientific advances reported in the literature for treating this disease. Solid tumors, including prostate cancer, breast cancer, and lung cancer remain highly prevalent among the world population. 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 publications WO 2021/028854, WO 2023/133201, and WO 2023/225141. 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 amine salts, crystalline forms, pharmaceutical compositions, their use in 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 compound represented by Formula I:



wherein X is L-tartaric acid, D-tartaric acid, fumaric acid, or salicylic acid, and R¹, R², and R³ are as defined in the detailed description. In certain embodiments, the compound is in crystalline form. Further description of additional features of the compounds are provided 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 method for treating a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2). The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I, to treat the disease or condition.

[0008] 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, to inhibit the activity of said NSD2.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1 depicts an X-ray powder diffractogram of crystalline L-tartaric acid salt of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-d₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol, as further described in Example 2.

[0010] FIG. 2 depicts a differential scanning calorimetry curve of crystalline L-tartaric acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol, as further described in Example 2.

[0011] FIG. 3 depicts an X-ray powder diffractogram of crystalline D-tartaric acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol, as further described in Example 3.

[0012] FIG. 4 depicts a differential scanning calorimetry curve of crystalline D-tartaric acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol, as further described in Example 3.

[0013] FIG. 5 depicts an X-ray powder diffractogram of crystalline fumaric acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol, as further described in Example 4.

[0014] FIG. 6 depicts a differential scanning calorimetry curve of crystalline fumaric acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol, as further described in Example 4.

[0015] FIG. 7 depicts an X-ray powder diffractogram of crystalline salicylic acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol, as further described in Example 5.

[0016] FIG. 8 depicts a differential scanning calorimetry curve of crystalline salicylic acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol, as further described in Example 5.

DETAILED DESCRIPTION

[0017] The invention provides deuterium-enriched piperidinyl-methyl-purine amine salts, crystalline forms, pharmaceutical compositions, their use in 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.

[0018] 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.

[0019] 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.

[0020] 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

[0021] 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.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] The term “lower haloalkyl” refers to a C₁₋₄ straight or branched alkyl group that is substituted with one or more halogen atoms.

[0026] 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 pyrrolidiny) or NR⁺ (as in N-substituted pyrrolidiny)).

[0027] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation.

[0028] 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.

[0029] 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.

[0030] 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.

[0031] The term “halogen” means F, Cl, Br, or I.

[0032] 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.

[0033] 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, quinolinyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indoliziny, 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, quinazolinyl, quinoxalyl, 4*H*-quinoliziny, 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.

[0034] 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).

[0035] 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, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, 2-oxa-6-azaspiro[3.3]heptane, and quinuclidinyl. The terms “heterocycle,” “heterocyclyl,” “heterocyclicyl”

ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indoliny, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinoliny. A heterocyclyl group may be mono- or bicyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0036] 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.

[0037] 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.

[0038] Each optional substituent on a substitutable carbon is a monovalent substituent independently selected from halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}$ -pyridyl which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-S(O)(NR^\circ)R^\circ$; $-$

$S(O)_2N=C(NR^\circ)_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ$; $-P(O)_2R^\circ$; $-P(O)R^\circ$; $-OP(O)R^\circ$; $-OP(O)(OR^\circ)_2$; SiR°_3 ; $-(C_{1-4}$ straight or branched alkylene) $O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^\circ)_2$.

[0039] 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 $-SSR^\bullet$.

[0040] 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 $=O$, $=S$, $=NNR^*$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, 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.

[0041] When R^* is C_{1-6} aliphatic, R^* is optionally substituted with halogen, $-R^\bullet$, $-(haloR^\bullet)$, $-OH$, $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein 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.

[0042] An optional substituent on a substitutable nitrogen is independently $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} 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 $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein when $R^{\dagger}$ is C_{1-6} aliphatic, $R^{\dagger}$ is optionally substituted with halogen, $-R^{\bullet}$, $-(haloR^{\bullet})$, $-OH$, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, $-CN$, $-C(O)OH$, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein 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.

[0043] 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 described in the literature. 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 compounds can include those derived from suitable inorganic and organic acids and bases.

[0044] 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] The terms “a” and “an” as used herein mean “one or more” and include the plural unless the context is inappropriate.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] The term “hydroxyalkyl” refers to an alkyl group that is substituted with at least one hydroxyl. Exemplary hydroxyalkyl groups include -CH₂CH₂OH, -C(H)(OH)CH₃, -CH₂C(H)(OH)CH₂CH₂OH, and the like.

[0054] 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.

[0055] The terms “alkoxyl” or “alkoxy” are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, *tert*-butoxy and the like. The term “haloalkoxyl” refers to an alkoxyl group that is substituted with at least one halogen. Exemplary haloalkoxyl groups include -OCH₂F, -OCHF₂, -OCF₃, -OCH₂CF₃, -OCF₂CF₃, and the like.

[0056] The term “oxo” is art-recognized and refers to a “=O” substituent. For example, a cyclopentane substituted with an oxo group is cyclopentanone.

[0057] The symbol “” indicates a point of attachment.

[0058] 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.

[0059] One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, 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. “Hydrate” is a solvate wherein the solvent molecule is H₂O.

[0060] 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.

[0061] 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%.

[0062] The term “IC₅₀” is art-recognized and refers to the concentration of a compound that is required to achieve 50% inhibition of the target.

[0063] 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. 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.

[0064] 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*.

[0065] 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].

[0066] For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are

non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

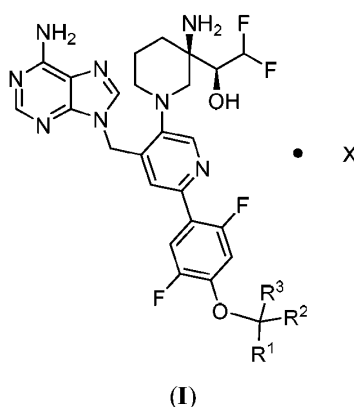
[0067] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention 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.

[0068] As a general matter, compositions specifying a percentage are by weight unless otherwise specified.

I. Salts of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

[0069] The invention provides salts of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol. The compounds are described in more detail below, which includes certain compounds that further comprise water. The compounds may be used in the pharmaceutical compositions and therapeutic methods described herein. Exemplary compounds are described in the following sections. Exemplary procedures for making the compounds are described in the Examples.

[0070] One aspect of the invention provides a compound represented by Formula I:



wherein:

X is L-tartaric acid, D-tartaric acid, fumaric acid, or salicylic acid;

R¹, R², and R³ are independently Z; and

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

[0071] 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).

[0072] In certain embodiments, the compound is a compound of Formula I.

[0073] As defined generally above, X is L-tartaric acid, D-tartaric acid, fumaric acid, or salicylic acid. In certain embodiments, X is L-tartaric acid. In certain embodiments, X is D-tartaric acid. In certain embodiments, X is fumaric acid. In certain embodiments, X is salicylic acid.

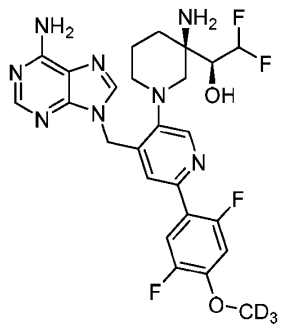
[0074] As defined generally above, R¹, R², and R³ are independently Z.

[0075] As defined generally above, Z is independently H or D, provided that the abundance of deuterium in Z is at least 75%. In certain embodiments, Z is independently H or D, provided that the abundance of deuterium in Z is at least 80%. In certain embodiments, Z is independently H or D, provided that the abundance of deuterium in Z is at least 85%. In certain embodiments, Z is independently H or D, provided that the abundance of deuterium in Z is at least 90%. In certain embodiments, Z is independently H or D, provided that the abundance of deuterium in Z is at least 92%. In certain embodiments, Z is independently H or D, provided that the abundance of deuterium in Z is at least 95%. In certain embodiments, Z is independently H or D, provided that the abundance of deuterium in Z is at least 97%. In certain embodiments, Z is independently H or D, provided that the abundance of deuterium in Z is at least 98%. In certain embodiments, Z is independently H or D, provided that the abundance of deuterium in Z is at least 99%. In certain embodiments, Z is D.

[0076] In certain embodiments, the mole ratio of X to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is about 1:1. In certain embodiments, the mole ratio of X to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is about 0.5:1. In certain embodiments, the mole ratio of X to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is from about 1: 1 to about 0.5:1.

A. L-Tartaric Acid Salt of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy- d_3)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

[0077] In certain embodiments, the compound is the L-tartaric acid salt of



[0078] In certain embodiments, the compound is in crystalline form. In certain embodiments, the crystalline form further comprises water. In certain embodiments, the crystalline form further comprises water, and the mole ratio of water to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy- d_3)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is in the range of about 0.75:1 to about 1.5:1. In certain embodiments, the crystalline form further comprises water, and the mole ratio of water to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy- d_3)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is about 1:1.

[0079] In certain embodiments, the compound is a hydrate of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy- d_3)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol L-tartaric acid salt. In certain embodiments, the compound is (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy- d_3)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol L-tartaric acid salt monohydrate.

[0080] In certain embodiments, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 16.1 ± 0.2 , 19.0 ± 0.2 , 19.2 ± 0.2 , 20.1 ± 0.2 , 20.7 ± 0.2 , 23.7 ± 0.2 , and 24.2 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 6.9 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 15.2 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 16.4 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 21.2 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 24.9 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 28.2 ± 0.2 .

[0081] In certain embodiments, the crystalline form exhibits an X-ray powder diffraction pattern comprising one or more peaks (or two or more peaks, or three or more peaks) selected from the following diffraction angles (2θ): 16.1 ± 0.2 , 19.0 ± 0.2 , 19.2 ± 0.2 , 20.1 ± 0.2 , 20.7 ± 0.2 , 23.7 ± 0.2 , and 24.2 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 6.9 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 15.2 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 16.4 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 21.2 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 24.9 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 28.2 ± 0.2 .

[0082] In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 5%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 10%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 15%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 20%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 25%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 30%.

[0083] In certain embodiments, the crystalline form is characterized by the following X-ray powder diffraction pattern expressed in terms of diffraction angle 2θ , inter-planar distances d , and relative intensity (expressed as a percentage with respect to the most intense peak):

Angle [2θ]	d-spacing [$\text{\AA}$]	Relative Intensity [%]
6.9	12.8	44
11.9	7.4	27
13.7	6.5	24
15.2	5.8	29
16.1	5.5	100
16.4	5.4	26
16.7	5.3	25
16.9	5.2	30
19.0	4.7	57
19.2	4.6	55
19.6	4.5	20
20.1	4.4	59
20.7	4.3	48
21.2	4.2	36
22.0	4.0	28

Angle [2 θ]	d-spacing [Å]	Relative Intensity [%]
22.4	4.0	29
23.0	3.9	20
23.7	3.8	51
24.2	3.7	57
24.9	3.6	36
28.2	3.2	23
29.3	3.1	23

[0084] In certain embodiments, the crystalline form is characterized as having an X-ray powder diffraction pattern substantially as shown in FIG. 1.

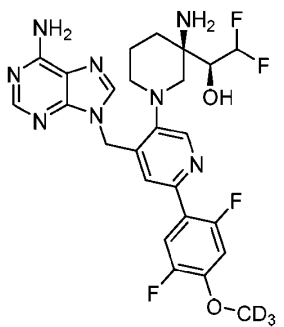
[0085] In certain embodiments, an X-ray powder diffraction pattern may be obtained using CuK α radiation. The temperature at which the X-ray powder diffraction pattern is obtained may be, for example, 25 ± 2 degrees Celsius.

[0086] In certain embodiments, the compound has a melting point onset as determined by differential scanning calorimetry in the range of from about 155 degrees Celsius to about 159 degrees Celsius. In certain embodiments, the compound has a melting point onset as determined by differential scanning calorimetry at about 157 degrees Celsius.

[0087] In certain embodiments, the compound has a differential scanning calorimetry curve substantially the same as shown in FIG. 2.

B. D-Tartaric Acid Salt of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-d₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

[0088] In certain embodiments, the compound is the D-tartaric acid salt of



[0089] In certain embodiments, the compound is in crystalline form. In certain embodiments, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2 θ): 6.0 ± 0.2 , 8.9 ± 0.2 , 10.6 ± 0.2 , 17.7 ± 0.2 , $20.9 \pm$

0.2, 21.5 ± 0.2 , and 24.0 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 15.4 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 16.0 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 29.9 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 30.3 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 33.0 ± 0.2 .

[0090] In certain embodiments, the crystalline form exhibits an X-ray powder diffraction pattern comprising one or more peaks (or two or more peaks, or three or more peaks) selected from the following diffraction angles (2θ): 6.0 ± 0.2 , 8.9 ± 0.2 , 10.6 ± 0.2 , 17.7 ± 0.2 , 20.9 ± 0.2 , 21.5 ± 0.2 , and 24.0 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 15.4 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 16.0 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 29.9 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 30.3 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 33.0 ± 0.2 .

[0091] In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 5%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 10%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 15%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 20%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 25%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 30%.

[0092] In certain embodiments, the crystalline form is characterized by the following X-ray powder diffraction pattern expressed in terms of diffraction angle 2θ , inter-planar distances d , and relative intensity (expressed as a percentage with respect to the most intense peak):

Angle [2θ]	d-spacing [$\text{\AA}$]	Relative Intensity [%]
6.0	14.6	43
8.9	10.0	42
10.6	8.4	69
15.4	5.8	32
16.0	5.6	32
17.7	5.0	65
20.9	4.3	100
21.5	4.1	52

Angle [2 θ]	d-spacing [Å]	Relative Intensity [%]
24.0	3.7	97
24.3	3.7	21
25.9	3.4	21
29.9	3.0	21
30.3	2.9	24
32.7	2.7	24
33.0	2.7	33

[0093] In certain embodiments, the crystalline form is characterized as having an X-ray powder diffraction pattern substantially as shown in FIG. 3.

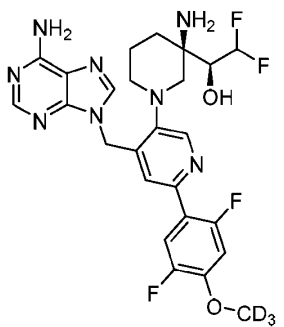
[0094] In certain embodiments, an X-ray powder diffraction pattern may be obtained using CuK α radiation. The temperature at which the X-ray powder diffraction pattern is obtained may be, for example, 25 ± 2 degrees Celsius.

[0095] In certain embodiments, the compound has a melting point onset as determined by differential scanning calorimetry in the range of from about 238 degrees Celsius to about 242 degrees Celsius. In certain embodiments, the compound has a melting point onset as determined by differential scanning calorimetry at about 240 degrees Celsius.

[0096] In certain embodiments, the compound has a differential scanning calorimetry curve substantially the same as shown in FIG. 4.

C. Fumaric Acid Salt of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-d₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

[0097] In certain embodiments, the compound is the fumaric acid salt of



[0098] In certain embodiments, the compound is in crystalline form. In certain embodiments, the crystalline form further comprises water. In certain embodiments, the crystalline form further comprises water, and the mole ratio of water to (S)-1-((R)-3-amino-1-

(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy- d_3)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is in the range of about 0.75:1 to about 1.5:1. In certain embodiments, the crystalline form further comprises water, and the mole ratio of water to (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy- d_3)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is about 1:1.

[0099] In certain embodiments, the compound is a hydrate of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy- d_3)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol fumaric acid salt. In certain embodiments, the compound is (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy- d_3)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol fumaric acid salt monohydrate.

[0100] In certain embodiments, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 16.5 ± 0.2 , 18.7 ± 0.2 , 20.7 ± 0.2 , 21.6 ± 0.2 , 22.7 ± 0.2 , 25.1 ± 0.2 , and 29.0 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 22.3 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 13.0 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 14.9 ± 0.2 .

[0101] In certain embodiments, the crystalline form exhibits an X-ray powder diffraction pattern comprising one or more peaks (or two or more peaks, or three or more peaks) selected from the following diffraction angles (2θ): 16.5 ± 0.2 , 18.7 ± 0.2 , 20.7 ± 0.2 , 21.6 ± 0.2 , 22.7 ± 0.2 , 25.1 ± 0.2 , and 29.0 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 22.3 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 13.0 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 14.9 ± 0.2 .

[0102] In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 5%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 10%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 15%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 20%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 25%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 30%.

[0103] In certain embodiments, the crystalline form is characterized by the following X-ray powder diffraction pattern expressed in terms of diffraction angle 2θ , inter-planar distances d , and relative intensity (expressed as a percentage with respect to the most intense peak):

Angle [2θ]	d-spacing [Å]	Relative Intensity [%]
13.0	6.82	22
14.9	5.94	28
16.5	5.38	100
18.7	4.73	41
20.7	4.29	40
21.6	4.11	64
22.3	3.98	30
22.7	3.92	93
25.1	3.55	70
29.0	3.08	64

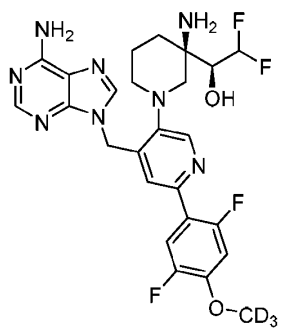
[0104] In certain embodiments, the crystalline form is characterized as having an X-ray powder diffraction pattern substantially as shown in FIG. 5.

[0105] In certain embodiments, the compound has a melting point onset as determined by differential scanning calorimetry in the range of from about 149 degrees Celsius to about 153 degrees Celsius. In certain embodiments, the compound has a melting point onset as determined by differential scanning calorimetry at about 151 degrees Celsius.

[0106] In certain embodiments, the compound has a differential scanning calorimetry curve substantially the same as shown in FIG. 6.

D. Salicylic Acid Salt of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-d₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

[0107] In certain embodiments, the compound is the salicylic acid salt of



[0108] In certain embodiments, the compound is in crystalline form. In certain embodiments, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 7.7 ± 0.2 , 13.6 ± 0.2 , 16.3 ± 0.2 , 20.4 ± 0.2 , 21.8 ± 0.2 , 22.5 ± 0.2 , and 25.2 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern

further comprises a peak at 12.5 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 16.1 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 17.2 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 19.7 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 29.5 ± 0.2 .

[0109] In certain embodiments, the crystalline form exhibits an X-ray powder diffraction pattern comprising one or more peaks (or two or more peaks, or three or more peaks) selected from the following diffraction angles (2θ): 7.7 ± 0.2 , 13.6 ± 0.2 , 16.3 ± 0.2 , 20.4 ± 0.2 , 21.8 ± 0.2 , 22.5 ± 0.2 , and 25.2 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 12.5 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 16.1 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 17.2 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 19.7 ± 0.2 . In certain embodiments, the X-ray powder diffraction pattern further comprises a peak at 29.5 ± 0.2 .

[0110] In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 5%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 10%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 15%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 20%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 25%. In certain embodiments, the relative intensity of the peak at said diffraction angles (2θ) is at least 30%.

[0111] In certain embodiments, the crystalline form is characterized by the following X-ray powder diffraction pattern expressed in terms of diffraction angle 2θ , inter-planar distances d , and relative intensity (expressed as a percentage with respect to the most intense peak):

Angle [2θ]	d-spacing [$\text{\AA}$]	Relative Intensity [%]
7.7	11.4	100
12.5	7.1	21
13.6	6.5	37
16.1	5.5	25
16.3	5.4	51
17.2	5.2	21
19.7	4.5	22
20.4	4.4	31
21.8	4.1	62

Angle [2θ]	d-spacing [Å]	Relative Intensity [%]
22.5	4.0	62
25.2	3.5	66
29.5	3.0	24

[0112] In certain embodiments, the crystalline form is characterized as having an X-ray powder diffraction pattern substantially as shown in FIG. 7.

[0113] In certain embodiments, an X-ray powder diffraction pattern may be obtained using CuK α radiation. The temperature at which the X-ray powder diffraction pattern is obtained may be, for example, 25 $\pm$ 2 degrees Celsius.

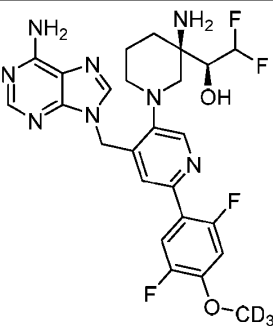
[0114] In certain embodiments, the compound has a melting point onset as determined by differential scanning calorimetry in the range of from about 204 degrees Celsius to about 208 degrees Celsius. In certain embodiments, the compound has a melting point onset as determined by differential scanning calorimetry at about 206 degrees Celsius.

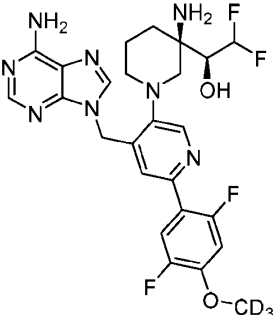
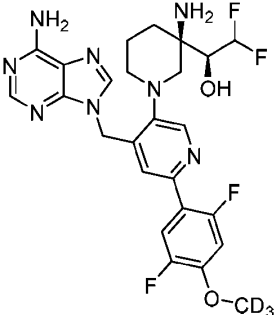
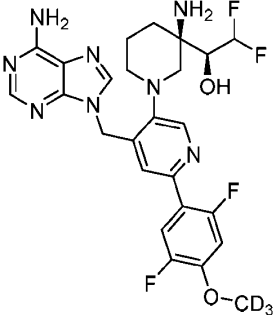
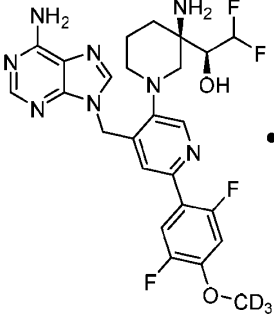
[0115] In certain embodiments, the mole ratio of salicylic acid to (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is about 0.5:1.

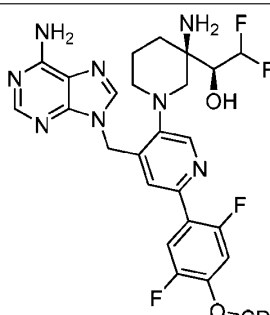
[0116] In certain embodiments, the compound has a differential scanning calorimetry curve substantially the same as shown in FIG. 8.

General Features

[0117] Another aspect of the invention provides a compound in Table 1-1 below.

Compound No.	Chemical Structure
I-1	 • L-tartaric acid

Compound No.	Chemical Structure
I-2	 • D-tartaric acid
I-3	 • fumaric acid
I-4	 • salicylic acid
I-5	 • L-tartaric acid • H₂O

Compound No.	Chemical Structure
I-6	 • fumaric acid • H₂O

[0118] Compounds may be characterized according to X-ray powder diffraction, thermogravimetric analysis, differential scanning calorimetry, ¹H NMR spectroscopy, and/or Karl Fischer (KF) titration.

[0119] For example, X-ray powder diffraction may be performed using either a Rigaku MiniFlex 600 or a Bruker D8 Advance equipped with LYNXEYE detector. Both instruments may be operated in reflection mode (*i.e.*, Bragg-Brentano geometry). Samples may be prepared on Si zero-return wafers. Exemplary parameters for XRPD using the Rigaku MiniFlex 600 are:

Parameter	Regular Scan	High-Resolution Scan
X-ray wavelength	Cu K α 1, 1.540598 Å	Cu K α 1, 1.540598 Å
X-ray tube setting	40 kV, 15 mA	40 kV, 15 mA
Slit condition	1.25 ° div., Ni k β filter, 0.3 mm rec.	1.25 ° div., Ni k β filter, 0.3 mm rec.
Scan mode	Continuous	Continuous
Scan range (°2 θ)	4-30	4-40
Step size (°2 θ)	0.05	0.05
Scan speed (°/min)	5	1.25
Spin	No	No

[0120] Exemplary parameters for XRPD using the Bruker D8 Advance are:

Parameter	Regular Scan	High-Resolution Scan
X-ray wavelength	Cu K α 1, 1.540598 Å	Cu K α 1, 1.540598 Å
X-ray tube setting	40 kV, 40 mA	40 kV, 40 mA
Slit condition	0.6 mm div. + 2.5 ° soller	0.6 mm div. + 2.5 ° soller
Scan mode	Step	Step
Scan range (°2 θ)	4-30	4-40
Step size (°2 θ)	0.03	0.02
Dwell time (s/step)	0.23	0.9
Spin	Yes (0.5 Hz)	Yes (0.5 Hz)

[0121] Simultaneous thermogravimetric analysis and differential scanning calorimetry may be performed using a Mettler Toledo TGA/DSC³⁺. Protective and purge gas may be nitrogen at a flow rate of 20-30 mL/min and 50-100 mL/min, respectively. The sample (5-10 mg) may be weighed directly into a hermetic aluminum pan with a pinhole and analyzed according to the following parameters: ramp method, heating rate 10.0 °C/min, and temperature range 30 to 300 °C.

[0122] Differential scanning calorimetry may be performed using a Mettler Toledo DSC³⁺ (with method gas flow of 60.00 mL/min) or a TA Discovery DSC (with method gas flow of 50.00 mL/min). With either instrument, the sample (1-5 mg) is weighed directly into a 40 µL hermetic aluminum pan with a pinhole and analyzed according to the following parameters: ramp method, heating rate 10.0 °C/min, temperature range 30 to 300 °C, and method gas N₂.

[0123] Dynamic vapor sorption may be performed using a Q5000SA. The sample (5-15 mg) is loaded into a metallic quartz sample pan, suspended from a microbalance, and exposed to a humidified stream of nitrogen gas. Weight changes are relative to a matching empty reference pan opposite the sample, suspended from the microbalance. The sample may be held for a minimum of 10 min at each humidity level and only progressed to the next humidity level if there is < 0.002 % change in weight between measurements (interval: 5 s) or 45 min had elapsed (for 5-65% RH) or 2 hours had elapsed (for 80 and 95% RH). The following program may be used:

1. Equilibration at 50 % RH
2. 50 % to 5 % (50 %, 35 %, 20 %, and 5 %)
3. 5 % to 95 % (5 %, 20 %, 35 %, 50 %, 65 %, 80 %, and 95 %)
4. 95 % to 5 % (95 %, 80 %, 65 %, 50 %, 35 %, 20 %, and 5 %)
5. 5 % to 50 % (5 %, 20 %, 35 %, and 50 %).

[0124] Karl Fischer (KF) titration for water determination may be performed using a Mettler Toledo C20S Coulometric KF Titrator equipped with a current generator cell with a diaphragm, and a double-platinum-pin electrode. AquastarTM CombiCoulomat fritless reagent may be used in both the anode and cathode compartments. Samples of approximately 0.03-0.10 g may be dissolved in the anode compartment and titrated until the solution potential dropped below 100 mV. Hydranal 1 wt % water standard may be used for validation prior to sample analysis.

[0125] Proton nuclear magnetic resonance (¹H NMR) spectroscopy may be performed on a Bruker Avance 400 MHz or 500 MHz spectrometer. Solids are dissolved in 0.60-0.75 mL of

deuterated solvent in a 4 mL vial, transferred to an NMR tube (Wilmad 5 mm thin wall 8" 200 MHz, 506-PP-8) and analyzed.

II. Therapeutic Applications of Salts of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

[0126] Compounds described herein, such as a compound of Formula **I**, or other compounds in Section I, provide therapeutic benefits to subjects suffering from cancer and other disorders. 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 to a subject in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula **I**, or other compounds in Section I, to treat the disease or condition. In certain embodiments, the particular compound is a compound defined by one of the embodiments described above.

[0127] 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.

[0128] In certain embodiments, said disease or condition mediated by NSD2 is cancer.

[0129] 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.

[0130] 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.

[0131] In certain embodiments, said disease or condition mediated by NSD2 is acute lymphoblastic leukemia, skin squamous cell carcinoma, or mantle cell lymphoma. In certain embodiments, said disease or condition mediated by NSD2 is acute lymphoblastic leukemia. 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.

[0132] 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.

[0133] 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.

[0134] 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.

[0135] 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.

[0136] In certain embodiments, said disease or condition mediated by NSD2 is myeloma.

[0137] 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.

[0138] 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.

[0139] 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.

[0140] Another aspect of the invention provides a compound described herein (such as a compound of Formula I, or other compounds in Section I) for use in treating a disease or condition described herein, such as cancer.

[0141] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I, 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.

[0142] Another aspect of the invention provides for the use of a compound described herein (such as a compound of Formula I, or other compounds in Section I) for treating a disease or condition, such as a disease or condition described herein (for example, cancer).

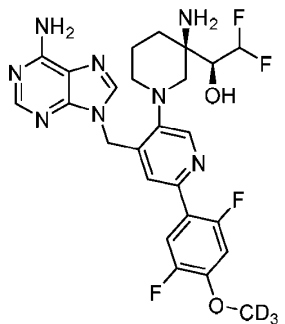
[0143] Further, compounds described herein, such as a compound of Formula I, or other compounds in Section I, inhibit the activity of nuclear SET domain-containing protein 2 (NSD2). Accordingly, another aspect of the invention provides a method of inhibiting the activity of nuclear SET domain-containing protein 2 (NSD2). The method comprises contacting a NSD2 with an effective amount of a compound described herein, such as a compound of Formula I, or other compounds in Section I, to inhibit the activity of said NSD2. In certain embodiments, the particular compound is a compound defined by one of the embodiments described above.

Evaluation of NSD2 Inhibitory Activity

[0144] The NSD2 inhibitory activity of a compound can be evaluated using a NSD2 inhibition assay, such as the NSD2 inhibition assay described herein below.

[0145] A reaction mixture can be prepared by adding oligonucleosomes from Chicken (0.05 mg/ml) to freshly prepared reaction buffer containing 50 mM Tris-HCl (pH 8.5), 50 mM NaCl, 5 mM MgCl₂, 0.01% Brij35, 1 mM DTT, and 1% DMSO followed by the addition of recombinant human NSD2, (amino acids 2-end) with N-terminal His tag (2 nM; GenBank Accession No. NM_001042424; MW=155.5 kDa; expressed in Sf9 insect cells) and gentle mixing. The test compound is diluted in DMSO, added to the reaction mixture in nanoliter amounts (using, e.g., Acoustic Technology (Echo 550, LabCyte Inc. Sunnyvale, CA)) and incubated for 20 minutes at room temperature. The reaction may be initiated by addition of S-Adenosyl-L-[methyl-³H] methionine (³H-SAM; 1 μ M), and the mixture is then incubated for 1 hour at 30°C. The reaction mixture can be delivered to filter paper and the methylated substrate quantified by scintillation counting. Data analysis may be performed using Excel and GraphPad Prism software for IC₅₀ curve fits. For additional information on the histone methyltransferase assay, see, for example, Horiuchi KY, *et al.*, "Assay Development for Histone Methyltransferases," Assay Drug Dev Technol. 2013 May;11(4):227-36.

[0146] The following compound had an IC₅₀ of less than 10 nM when evaluated using the above NSD2 inhibition assay:



III. Combination Therapy

[0147] Another aspect of the invention provides for combination therapy. Compounds described herein (e.g., a compound of Formula I, or other compounds in Section I) may be used in combination with additional therapeutic agents to treat a disease or condition, such as a cancer.

[0148] 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.

[0149] 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.

[0150] 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.

[0151] 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 to erlotinib, bortezomib, fulvestrant, sunitinib, 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, ibritumomab, abagovomab, adecatumumab, afutuzumab, alacizumab, alemtuzumab, anatumomab, apolizumab, bavixumab, belimumab, bivatuzumab mertansine, blinatumomab, brentuximab vedotin, cantuzumab mertansine, catumazumab, cetuximab, citatuzumab bogatox, cixutumumab, clivatuzumab tetraxetan, conatumumab, dacetuzumab, daclizumab, detumomab, ecomeximab, edrecolomab, elotuzumab, epratuzumab, ertumaxomab, etaracizumab, farletuzumab, figitumumab, fresolimumab, galiximab, gemtatumumab vedotin, gemtuzumab, ibritumomab tiuxetan, inotuzumab ozogamicin, intetumumab, ipilimumab, iratumumab, labetuzumab, lexatumumab, lintuzumab, lucatumumab, lumiliximab, 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 paptax, tenatumumab, 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-HM1.24, 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).

[0152] 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®), tezacitibine, gemcitabine (difluorodeoxycytidine), hydroxyurea (HYDREA®), idarubicin (IDAMYCIN®), ifosfamide (IFEX®), irinotecan (CAMPTOSAR®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (ALKERAN®), 6-mercaptopurine (PURINETHOL®), methotrexate (FOLEX®), mitoxantrone (NOVANTRONE®), gcmtuzumab 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®).

[0153] 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 vemurafenib, 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.

[0154] 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™), vemurafenib (e.g., ZELBORAF®), and ipilimumab (e.g., YERVOY®).

[0155] 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®).

[0156] For the treatment of thyroid cancer, the additional therapeutic agent is selected from doxorubicin hydrochloride (Adriamycin®), cabozantinib-S-malate (COMETRIQ®), and vandetanib (CAPRELSA®).

[0157] 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®).

[0158] 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®).

[0159] 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 (MITOZYTREX™, MUTAMYCIN®).

[0160] For the treatment of cervical cancer, the additional therapeutic agent is selected from bleomycin (BLENOXANE®), cisplatin (PLATINOL®, PLATINOL-AQ®), and topotecan hydrochloride (HYCAMTIN®).

[0161] 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®).

[0162] 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®).

[0163] 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®).

[0164] 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 (ZOFTRAN®), granisetron HCl (KYTRIL®), lorazepam (ATIVAN®), dexamethasone (DECADRON®), prochlorperazine (COMPAZINE®), casopitant (REZONIC® and Zunrisa®), and combinations thereof.

[0165] 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.

[0166] 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).

[0167] 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.

[0168] 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 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 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 other compounds in Section I) and the additional therapeutic agent(s) are present in the same composition, which is suitable for oral administration.

[0169] In certain embodiments, the compound described herein (e.g., a compound of Formula I, 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.

[0170] 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 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

[0171] 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 other compounds in Section I) and a pharmaceutically acceptable carrier.

[0172] 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.

[0173] 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.

[0174] 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.

[0175] 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.

[0176] 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.

[0177] 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.

[0178] 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.

[0179] 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.

[0180] 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.

[0181] 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.

[0182] 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.

[0183] 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.

[0184] 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.

[0185] 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.

[0186] 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.

[0187] 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.

[0188] 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.

[0189] 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.

[0190] 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.

[0191] 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.

[0192] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[0193] 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.

[0194] 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.

[0195] 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.

[0196] 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.

[0197] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[0198] 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.

[0199] 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.

[0200] 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.

[0201] 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.

[0202] 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.

[0203] 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.

[0204] 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.

[0205] 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.

[0206] 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.

[0207] 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.

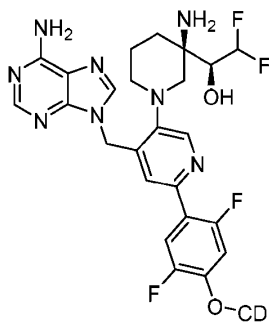
[0208] If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. Preferred dosing is one administration per day.

[0209] The invention further provides a unit dosage form (such as a tablet or capsule) comprising a compound described herein in a therapeutically effective amount for the treatment of a disease or condition described herein.

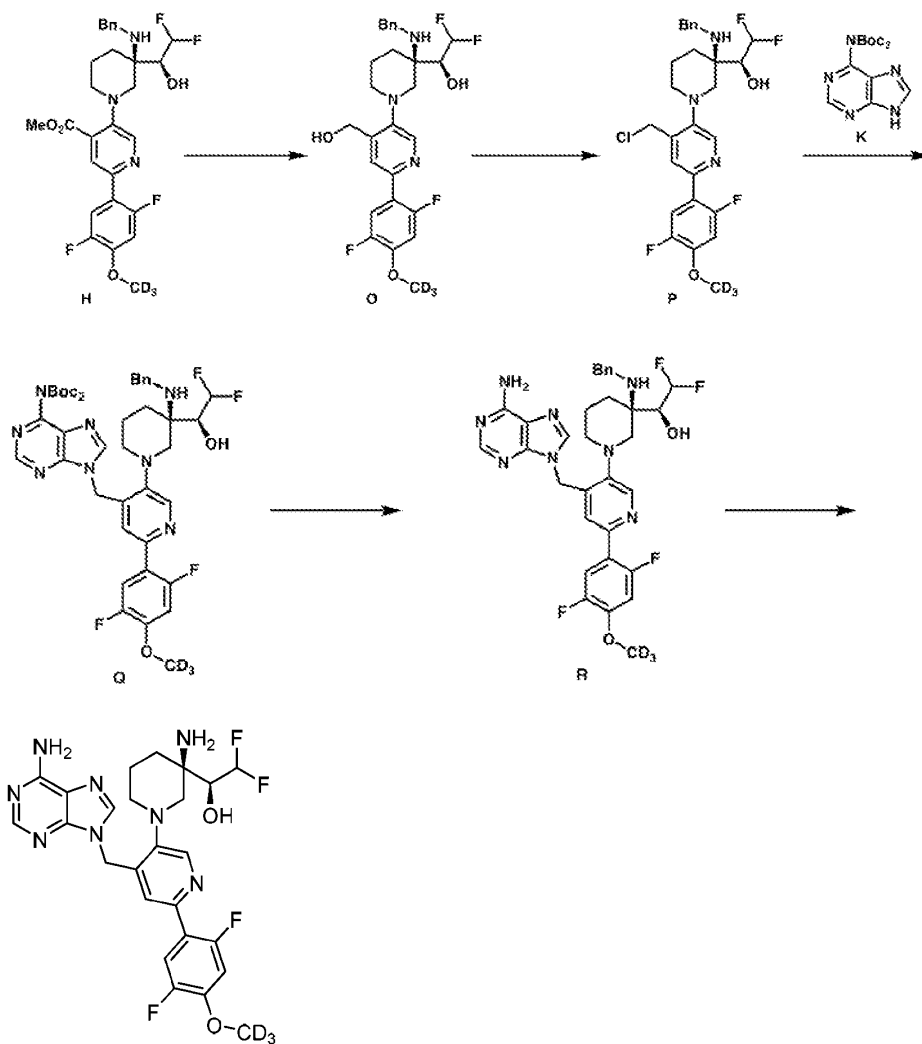
EXAMPLES

[0210] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention. Starting materials described herein can be obtained from commercial sources or may be readily prepared from commercially available materials using transformations known to those of skill in the art.

EXAMPLE 1 – Preparation of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol (Compound II-1)



[0211] The title compound was prepared using the following procedures.



II-1

[0212] Part 1: Preparation of Compound O. To a solution of compound **H** (33.0 g, 1.00 eq) in THF (297 mL) and MeOH (33.0 mL) was added LiBH_4 (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 with water (100 mL), and the resulting mixture was extracted with EtOAc (50.0 mL x 3). The organic phase was isolated, washed with brine (200 mL), dried over anhydrous Na_2SO_4 , and concentrated under vacuum to provide compound **O** (29.0 g) as a white solid. ^1H NMR: (DMSO- d_6 , 400 MHz) 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.

[0213] Part 2: Preparation of Compound P. 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. 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 with aqueous 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 , 400 MHz) 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.

[0214] Part 3: Preparation of Compound Q. To a solution of compound **P** (29.0 g, 1.00 eq) and compound **K** (18.0 g, 1.30 eq) in dimethyl acetamide (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 with H_2O (200 mL) at 0 °C to 5 °C and 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.

[0215] Part 4: Preparation of Compound R. 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 poured into aqueous Na_2CO_3 (50.0 mL). A solid precipitated from solution and 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: ($\text{DMSO}-d_6$, 400 MHz) 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.

[0216] Part 5: Preparation of Compound II-1. To a solution of compound **R** (14.00 g, 1.00 eq) in THF (70.0 mL) was added $\text{Pd}(\text{OH})_2$ (1.40 g, 10%) and TFA (7.48 g, 3.00 eq) under N_2

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 **II-1** (6.70 g) as an off-white solid. ¹H NMR: (DMSO-*d*₆, 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, 4 H), 1.47 (s, 1H). MS (ES API+), 550.0, calc'd 550.2 (M+H⁺).

EXAMPLE 2 – Preparation of L-tartaric acid salt of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

[0217] (S)-1-((R)-3-Amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol (200.2 mg) was charged to a vial followed by L-tartaric acid (60.2 mg). To the vial, acetonitrile/water (3 mL, 9/1, v/v) was added, and the resulting suspension was heated to 50 °C and held at this temperature for one hour. Then, an additional charge of acetonitrile/water (5 mL, 9/1, v/v) was added to the thick slurry, and the resulting slurry was cooled to ambient temperature. Solids in the resulting mixture were collected by filtration and then dried in a vacuum oven to provide the title compound as a crystalline solid. In the crystalline solid, the mole ratio of L-tartaric acid to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol was about 1:1.

[0218] An X-ray powder diffractogram of the crystalline solid is provided in FIG. 1. Tabulated characteristics of the X-ray powder diffractogram in FIG. 1 are provided in Table 1, which lists diffraction angle 2 θ , inter-planar distances *d*, and relative intensity (expressed as a percentage with respect to the most intense peak):

TABLE 1. X-RAY POWDER DIFFRACTOGRAM DATA

Angle [2 θ]	<i>d</i> -spacing [Å]	Relative Intensity [%]
6.9	12.8	44
11.9	7.4	27
13.7	6.5	24
15.2	5.8	29
16.1	5.5	100

Angle [2θ]	d-spacing [Å]	Relative Intensity [%]
16.4	5.4	26
16.7	5.3	25
16.9	5.2	30
19.0	4.7	57
19.2	4.6	55
19.6	4.5	20
20.1	4.4	59
20.7	4.3	48
21.2	4.2	36
22.0	4.0	28
22.4	4.0	29
23.0	3.9	20
23.7	3.8	51
24.2	3.7	57
24.9	3.6	36
28.2	3.2	23
29.3	3.1	23

[0219] A differential scanning calorimetry curve of the crystalline solid is provided in FIG. 2.

[0220] The crystalline form has an endotherm with onsets as determined by differential scanning calorimetry of about 57.54 degrees Celsius (127.74 J/g) and 156.96 degrees Celsius (18.51 J/g).

[0221] The crystalline solid was analyzed for water content by KF titration and determined to have a water content of 2.33 wt % (*i.e.*, approximately 0.93 molar equivalents relative to L-tartaric acid salt).

[0222] The crystalline solid was analyzed by ¹H NMR spectroscopy. ¹H NMR: (400 MHz, DMSO-*d*₆) δ 8.53 (s, 1H), 8.25 (s, 1H), 8.16 (s, 1H), 7.71-7.66 (m, 1H), 7.33 (s, 2H), 7.16-7.11 (m, 1H), 7.04 (s, 1H), 6.28 (t, *J* = 56.0 Hz, 1H), 5.63-5.54 (m, 2H), 4.01 (s, 2H), 3.98 (br s, 1H), 3.18-2.89 (m, 4H), 1.92-1.74 (m, 4 H).

[0223] The crystalline form had a weight loss of about 4.97% when subjected to thermogravimetric analysis from 32 degrees Celsius to 152 degrees Celsius. The crystalline form had a weight loss of about 0.15% when subjected to thermogravimetric analysis from 155 degrees Celsius to 174 degrees Celsius. The crystalline form had a weight loss of about 2.32% when subjected to thermogravimetric analysis from 174 degrees Celsius to 205 degrees Celsius.

EXAMPLE 3 – Preparation of D-tartaric acid salt of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

[0224] (S)-1-((R)-3-Amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol (200.3 mg) was charged to a vial followed by ethanol (4 mL). The resulting suspension was heated to 50 °C, and D-tartaric acid (60.4 mg) dissolved in water (0.2 mL) was added slowly to the mixture. The resulting mixture was stirred overnight at 50 °C. Then, the mixture was cooled to ambient temperature. Solids in the resulting mixture were collected by filtration and then dried in a vacuum oven to provide the title compound as a crystalline solid. In the crystalline solid, the mole ratio of D-tartaric acid to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol was about 1:1.

[0225] An X-ray powder diffractogram of the crystalline solid is provided in FIG. 3. Tabulated characteristics of the X-ray powder diffractogram in FIG. 3 are provided in Table 2, which lists diffraction angle 2θ, inter-planar distances d, and relative intensity (expressed as a percentage with respect to the most intense peak):

TABLE 2. X-RAY POWDER DIFFRACTOGRAM DATA

Angle [2θ]	d-spacing [Å]	Relative Intensity [%]
6.0	14.6	43
8.9	10.0	42
10.6	8.4	69
15.4	5.8	32
16.0	5.6	32
17.7	5.0	65
20.9	4.3	100
21.5	4.1	52
24.0	3.7	97
24.3	3.7	21
25.9	3.4	21
29.9	3.0	21
30.3	2.9	24
32.7	2.7	24
33.0	2.7	33

[0226] A differential scanning calorimetry curve of the crystalline solid is provided in FIG. 4.

[0227] The crystalline form has an endotherm with an onset as determined by differential scanning calorimetry of about 240.09 degrees Celsius (268.63 J/g).

[0228] The crystalline solid was analyzed for water content by KF titration and determined to have a water content of 0.42 wt % (*i.e.*, approximately 0.16 molar equivalents relative to *D*-tartaric acid salt).

[0229] The crystalline solid was analyzed by ¹H NMR spectroscopy. ¹H NMR: (400 MHz, DMSO-*d*₆) δ 8.53 (s, 1H), 8.25 (s, 1H), 8.16 (s, 1H), 7.71-7.66 (m, 1H), 7.33 (s, 2H), 7.16-7.11 (m, 1H), 7.04 (s, 1H), 6.27 (t, *J* = 56.0 Hz, 1H), 5.63-5.54 (m, 2H), 4.01 (s, 2H), 3.97 (br s, 1H), 3.18-3.16 (m, 1H), 3.06-2.89 (m, 3H), 1.91-1.74 (m, 4 H).

[0230] The crystalline form had a weight loss of about 0.37% when subjected to thermogravimetric analysis from 45 degrees Celsius to 220 degrees Celsius. The crystalline form had a weight loss of about 15.16% when subjected to thermogravimetric analysis from 224 degrees Celsius to 270 degrees Celsius.

EXAMPLE 4 – Preparation of fumaric acid salt of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

[0231] (S)-1-((R)-3-Amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol (200.5 mg) was charged to a vial followed by fumaric acid (46.8 mg). To the vial, isopropanol/water (3.8 mL, 9/1, v/v) was added, and the resulting suspension was heated to 50 °C and held at this temperature for two hours. Then, the reaction slurry was cooled to ambient temperature and stirred overnight. Solids in the resulting mixture were collected by filtration and then dried in a vacuum oven to provide the title compound as a crystalline solid. In the crystalline solid, the mole ratio of fumaric acid to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol was about 1:1.

[0232] An X-ray powder diffractogram of the crystalline solid is provided in FIG. 5. Tabulated characteristics of the X-ray powder diffractogram in FIG. 5 are provided in Table 3, which lists diffraction angle 2θ, inter-planar distances *d*, and relative intensity (expressed as a percentage with respect to the most intense peak):

TABLE 3. X-RAY POWDER DIFFRACTOGRAM DATA

Angle [2 θ]	d-spacing [Å]	Relative Intensity [%]
13.0	6.8	22
14.9	5.9	28
16.5	5.4	100
18.7	4.7	41
20.7	4.3	40
21.6	4.1	64
22.3	4.0	30
22.7	3.9	93
25.1	3.6	70
29.0	3.1	64

[0233] A differential scanning calorimetry curve of the crystalline solid is provided in FIG. 6.

[0234] The crystalline form has an endotherm with onsets as determined by differential scanning calorimetry of about 97.42 degrees Celsius (119.62 J/g) and 150.50 degrees Celsius (23.11 J/g).

[0235] The crystalline solid was analyzed for water content by KF titration and determined to have a water content of 2.86 wt % (*i.e.*, approximately 1.08 molar equivalents relative to fumaric acid salt).

[0236] The crystalline solid was analyzed by ^1H NMR spectroscopy. ^1H NMR: (400 MHz, DMSO- d_6) δ 8.52 (s, 1H), 8.25 (s, 1H), 8.15 (s, 1H), 7.71-7.66 (m, 1H), 7.32 (br s, 2H), 7.15-7.10 (m, 1H), 7.01 (s, 1H), 6.54 (s, 2H), 6.25 (t, J = 56.0 Hz, 1H), 5.63-5.54 (m, 2H), 3.91 (br m, 1H), 3.16-2.88 (m, 4H), 1.93-1.72 (m 4H).

[0237] The crystalline form had a weight loss of about 1.93% when subjected to thermogravimetric analysis from 40 degrees Celsius to 115 degrees Celsius. The crystalline form had a weight loss of about 2.11% when subjected to thermogravimetric analysis from 115 degrees Celsius to 145 degrees Celsius. The crystalline form had a weight loss of about 8.04% when subjected to thermogravimetric analysis from 180 degrees Celsius to 258 degrees Celsius.

EXAMPLE 5 – Preparation of salicylic acid salt of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol

[0238] (S)-1-((R)-3-Amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol (200.3 mg) was charged to a vial and dissolved in THF (4 mL). The vial was then charged with salicylic acid (50.6 mg) in ethanol (1.5 mL). The resulting mixture was heated to 45 °C and allowed to evaporate. Then, the vial was charged with methyl isobutyl ketone (MIBK) (2 mL), and the vial contents were heated to 50 °C. Then, additional MIBK (1.4 mL) was added to the vial, and the resulting slurry was cooled to ambient temperature and then stirred overnight. Solids in the resulting mixture were collected by filtration and dried in a vacuum oven to provide the title compound as a crystalline solid.

[0239] An X-ray powder diffractogram of the crystalline solid is provided in FIG. 7. Tabulated characteristics of the X-ray powder diffractogram in FIG. 7 are provided in Table 4, which lists diffraction angle 2θ, inter-planar distances d, and relative intensity (expressed as a percentage with respect to the most intense peak):

TABLE 4. X-RAY POWDER DIFFRACTOGRAM DATA

Angle [2θ]	d-spacing [Å]	Relative Intensity [%]
7.7	11.4	100
12.5	7.1	21
13.6	6.5	37
16.1	5.5	25
16.3	5.4	51
17.2	5.2	21
19.7	4.5	22
20.4	4.4	31
21.8	4.1	62
22.5	4.0	62
25.2	3.5	66
29.5	3.0	24

[0240] A differential scanning calorimetry curve of the crystalline solid is provided in FIG. 8.

[0241] The crystalline form has an endotherm with an onset as determined by differential scanning calorimetry of about 205.53 degrees Celsius (81.792 J/g).

[0242] The crystalline solid was analyzed for water content by KF titration and determined to have a water content of < 0.1 wt %.

[0243] The crystalline solid was analyzed by ¹H NMR spectroscopy and determined to have a 1:0.5 molar ratio of (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol to salicylic acid salt. ¹H NMR: (500 MHz, DMSO-*d*₆) δ 8.53 (s, 1H), 8.24 (s, 1H), 8.16 (s, 1H), 7.71-7.63 (m, 1.5H), 7.33 (s, 2H), 7.15-7.10 (m, 1.5H), 7.03 (s, 1H), 6.61-6.55 (m, 1H), 6.27 (t, *J* = 56.0 Hz, 1H), 5.59-5.55 (br s, 2H), 3.95 (br s, 1H), 3.20-2.90 (m, 4H), 1.92-1.75 (m, 4H).

[0244] The crystalline form had a weight loss of about 1.23% when subjected to thermogravimetric analysis from 45 degrees Celsius to 200 degrees Celsius. The crystalline form had a weight loss of about 1.11% when subjected to thermogravimetric analysis from 200 degrees Celsius to 220 degrees Celsius. The crystalline form had a weight loss of about 11.32% when subjected to thermogravimetric analysis from 220 degrees Celsius to 285 degrees Celsius.

INCORPORATION BY REFERENCE

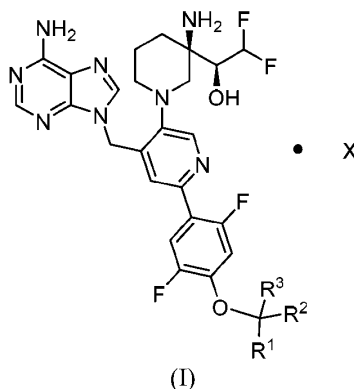
[0245] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0246] 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:



wherein:

X is L-tartaric acid, D-tartaric acid, fumaric acid, or salicylic acid;

R¹, R², and R³ are independently Z; and

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

2. The compound of claim 1, wherein the Z is D.
3. The compound of claim 1 or 2, wherein the mole ratio of X to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is about 1:1.
4. The compound of claim 1 or 2, wherein the mole ratio of X to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is about 0.5:1.
5. The compound of any one of claims 1-3, wherein X is L-tartaric acid.
6. The compound of claim 5, wherein the compound is in crystalline form.
7. The compound of claim 6, wherein the crystalline form further comprises water.
8. The compound of claim 7, wherein the mole ratio of water to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is in the range of about 0.75:1 to about 1.5:1.
9. The compound of claim 7, wherein the mole ratio of water to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is about 1:1.

10. The compound of claim 7, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 16.1 ± 0.2 , 19.0 ± 0.2 , 19.2 ± 0.2 , 20.1 ± 0.2 , 20.7 ± 0.2 , 23.7 ± 0.2 , and 24.2 ± 0.2 .
11. The compound of claim 10, wherein the X-ray powder diffraction pattern further comprises a peak at 6.9 ± 0.2 .
12. The compound of claim 10 or 11, wherein the X-ray powder diffraction pattern further comprises a peak at 15.2 ± 0.2 .
13. The compound of any one of claims 10-12, wherein the X-ray powder diffraction pattern further comprises a peak at 16.4 ± 0.2 .
14. The compound of any one of claims 10-13, wherein the X-ray powder diffraction pattern further comprises a peak at 21.2 ± 0.2 .
15. The compound of any one of claims 10-14, wherein the X-ray powder diffraction pattern further comprises a peak at 24.9 ± 0.2 .
16. The compound of any one of claims 10-15, wherein the X-ray powder diffraction pattern further comprises a peak at 28.2 ± 0.2 .
17. The compound of any one of claims 10-16, wherein the relative intensity of the peak at said diffraction angles (2θ) is at least 15%.
18. The compound of any one of claims 10-16, wherein the relative intensity of the peak at said diffraction angles (2θ) is at least 20%.
19. The compound of claim 7, characterized by the following X-ray powder diffraction pattern expressed in terms of diffraction angle 2θ , inter-planar distances d , and relative intensity (expressed as a percentage with respect to the most intense peak):

Angle [2θ]	d-spacing [$\text{\AA}$]	Relative Intensity [%]
6.9	12.8	44
11.9	7.4	27
13.7	6.5	24
15.2	5.8	29
16.1	5.5	100
16.4	5.4	26
16.7	5.3	25
16.9	5.2	30
19.0	4.7	57
19.2	4.6	55

Angle [2 θ]	d-spacing [Å]	Relative Intensity [%]
19.6	4.5	20
20.1	4.4	59
20.7	4.3	48
21.2	4.2	36
22.0	4.0	28
22.4	4.0	29
23.0	3.9	20
23.7	3.8	51
24.2	3.7	57
24.9	3.6	36
28.2	3.2	23
29.3	3.1	23

20. The compound of claim 7, wherein the X-ray powder diffraction pattern is substantially as shown in FIG. 1.
21. The compound of any one of claims 5-20, wherein the compound has a melting point onset as determined by differential scanning calorimetry in the range of from about 155 degrees Celsius to about 159 degrees Celsius.
22. The compound of any one of claims 5-20, wherein the compound has a melting point onset as determined by differential scanning calorimetry at about 157 degrees Celsius.
23. The compound of any one of claims 5-20, wherein the compound has a differential scanning calorimetry curve substantially the same as shown in FIG. 2.
24. The compound of any one of claims 1-3, wherein X is D-tartaric acid.
25. The compound of claim 24, wherein the compound is in crystalline form.
26. The compound of claim 25, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2 θ): 6.0 ± 0.2 , 8.9 ± 0.2 , 10.6 ± 0.2 , 17.7 ± 0.2 , 20.9 ± 0.2 , 21.5 ± 0.2 , and 24.0 ± 0.2 .
27. The compound of claim 26, wherein the X-ray powder diffraction pattern further comprises a peak at 15.4 ± 0.2 .
28. The compound of claim 26 or 27, wherein the X-ray powder diffraction pattern further comprises a peak at 16.0 ± 0.2 .
29. The compound of any one of claims 26-28, wherein the X-ray powder diffraction pattern further comprises a peak at 29.9 ± 0.2 .

30. The compound of any one of claims 26-29, wherein the X-ray powder diffraction pattern further comprises a peak at 30.3 ± 0.2 .
31. The compound of any one of claims 26-30, wherein the X-ray powder diffraction pattern further comprises a peak at 33.0 ± 0.2 .
32. The compound of any one of claims 26-31, wherein the relative intensity of the peak at said diffraction angles (2θ) is at least 15%.
33. The compound of any one of claims 26-31, wherein the relative intensity of the peak at said diffraction angles (2θ) is at least 20%.
34. The compound of claim 25, characterized by the following X-ray powder diffraction pattern expressed in terms of diffraction angle 2θ , inter-planar distances d , and relative intensity (expressed as a percentage with respect to the most intense peak):

Angle [2θ]	d-spacing [$\text{\AA}$]	Relative Intensity [%]
6.0	14.6	43
8.9	10.0	42
10.6	8.4	69
15.4	5.8	32
16.0	5.6	32
17.7	5.0	65
20.9	4.3	100
21.5	4.1	52
24.0	3.7	97
24.3	3.7	21
25.9	3.4	21
29.9	3.0	21
30.3	2.9	24
32.7	2.7	24
33.0	2.7	33

35. The compound of claim 25, wherein the X-ray powder diffraction pattern is substantially as shown in FIG. 3.
36. The compound of any one of claims 24-35, wherein the compound has a melting point onset as determined by differential scanning calorimetry in the range of from about 238 degrees Celsius to about 242 degrees Celsius.
37. The compound of any one of claims 24-35, wherein the compound has a melting point onset as determined by differential scanning calorimetry at about 240 degrees Celsius.

38. The compound of any one of claims 24-35, wherein the compound has a differential scanning calorimetry curve substantially the same as shown in FIG. 4.
39. The compound of any one of claims 1-3, wherein X is fumaric acid.
40. The compound of claim 39, wherein the compound is in crystalline form.
41. The compound of claim 40, wherein the crystalline form further comprises water.
42. The compound of claim 41, wherein the mole ratio of water to (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is in the range of about 0.75:1 to about 1.5:1.
43. The compound of claim 41, wherein the mole ratio of water to (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is about 1:1.
44. The compound of claim 41, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 16.5 ± 0.2 , 18.7 ± 0.2 , 20.7 ± 0.2 , 21.6 ± 0.2 , 22.7 ± 0.2 , 25.1 ± 0.2 , and 29.0 ± 0.2 .
45. The compound of claim 44, wherein the X-ray powder diffraction pattern further comprises a peak at 22.3 ± 0.2 .
46. The compound of claim 44 or 45, wherein the X-ray powder diffraction pattern further comprises a peak at 13.0 ± 0.2 .
47. The compound of any one of claims 44-46, wherein the X-ray powder diffraction pattern further comprises a peak at 14.9 ± 0.2 .
48. The compound of any one of claims 44-47, wherein the relative intensity of the peak at said diffraction angles (2θ) is at least 15%.
49. The compound of any one of claims 44-47, wherein the relative intensity of the peak at said diffraction angles (2θ) is at least 20%.
50. The compound of claim 41, characterized by the following X-ray powder diffraction pattern expressed in terms of diffraction angle 2θ , inter-planar distances *d*, and relative intensity (expressed as a percentage with respect to the most intense peak):

Angle [2θ]	<i>d</i> -spacing [Å]	Relative Intensity [%]
13.0	6.8	22
14.9	5.9	28
16.5	5.4	100

Angle [2 θ]	d-spacing [Å]	Relative Intensity [%]
18.7	4.7	41
20.7	4.3	40
21.6	4.1	64
22.3	4.0	30
22.7	3.9	93
25.1	3.6	70
29.0	3.1	64

51. The compound of claim 41, wherein the X-ray powder diffraction pattern is substantially as shown in FIG. 5.
52. The compound of any one of claims 39-51, wherein the compound has a melting point onset as determined by differential scanning calorimetry in the range of from about 149 degrees Celsius to about 153 degrees Celsius.
53. The compound of any one of claims 39-51, wherein the compound has a melting point onset as determined by differential scanning calorimetry at about 151 degrees Celsius.
54. The compound of any one of claims 39-51, wherein the compound has a differential scanning calorimetry curve substantially the same as shown in FIG. 6.
55. The compound of any one of claims 1, 2, or 4, wherein X is salicylic acid.
56. The compound of claim 55, wherein the compound is in crystalline form.
57. The compound of claim 56, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2 θ): 7.7 ± 0.2 , 13.6 ± 0.2 , 16.3 ± 0.2 , 20.4 ± 0.2 , 21.8 ± 0.2 , 22.5 ± 0.2 , and 25.2 ± 0.2 .
58. The compound of claim 57, wherein the X-ray powder diffraction pattern further comprises a peak at 12.5 ± 0.2 .
59. The compound of claim 57 or 58, wherein the X-ray powder diffraction pattern further comprises a peak at 16.1 ± 0.2 .
60. The compound of any one of claims 57-59, wherein the X-ray powder diffraction pattern further comprises a peak at 17.2 ± 0.2 .
61. The compound of any one of claims 57-60, wherein the X-ray powder diffraction pattern further comprises a peak at 19.7 ± 0.2 .

62. The compound of any one of claims 57-61, wherein the X-ray powder diffraction pattern further comprises a peak at 29.5 ± 0.2 .
63. The compound of any one of claims 57-62, wherein the relative intensity of the peak at said diffraction angles (2θ) is at least 15%.
64. The compound of any one of claims 57-62, wherein the relative intensity of the peak at said diffraction angles (2θ) is at least 20%.
65. The compound of claim 56, characterized by the following X-ray powder diffraction pattern expressed in terms of diffraction angle 2θ , inter-planar distances d , and relative intensity (expressed as a percentage with respect to the most intense peak):

Angle [2θ]	d-spacing [$\text{\AA}$]	Relative Intensity [%]
7.7	11.4	100
12.5	7.1	21
13.6	6.5	37
16.1	5.5	25
16.3	5.4	51
17.2	5.2	21
19.7	4.5	22
20.4	4.4	31
21.8	4.1	62
22.5	4.0	62
25.2	3.5	66
29.5	3.0	24

66. The compound of claim 56, wherein the X-ray powder diffraction pattern is substantially as shown in FIG. 7.
67. The compound of any one of claims 55-66, wherein the compound has a melting point onset as determined by differential scanning calorimetry in the range of from about 204 degrees Celsius to about 208 degrees Celsius.
68. The compound of any one of claims 55-66, wherein the compound has a melting point onset as determined by differential scanning calorimetry at about 206 degrees Celsius.
69. The compound of any one of claims 55-66, wherein the compound has a differential scanning calorimetry curve substantially the same as shown in FIG. 8.

70. The compound of claim 56, wherein the mole ratio of salicylic acid to (S)-1-((R)-3-amino-1-(4-((6-amino-9H-purin-9-yl)methyl)-6-(2,5-difluoro-4-(methoxy-*d*₃)phenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is about 0.5:1.
71. A pharmaceutical composition comprising a compound of any one of claims 1-70 and a pharmaceutically acceptable carrier.
72. 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 1-70 to treat the disease or condition.
73. The method of claim 72, wherein said disease or condition mediated by NSD2 is cancer.
74. The method of claim 72, wherein said disease or condition mediated by NSD2 is selected from solid tumors, leukemia, myeloma, lymphoma, and hypertension.
75. The method of claim 72, 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.
76. The method of claim 72, wherein said disease or condition mediated by NSD2 is acute lymphoblastic leukemia, skin squamous cell carcinoma, or mantle cell lymphoma.
77. The method of claim 72, wherein said disease or condition mediated by NSD2 is prostate cancer.
78. The method of any one of claims 72-77, wherein the subject is a human.
79. 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 1-70 to inhibit the activity of said NSD2.