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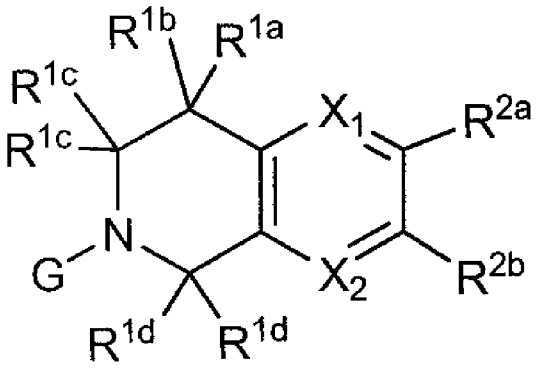
(54) Title: SUBSTITUTED HYDROXAMIC ACIDS AND USES THEREOF



(I)

(57) Abstract: This invention provides compounds of formula (I): wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{2a}, R^{2b}, X_1 X_2, and G have values as described in the specification, useful as inhibitors of HDAC6. The invention also provides pharmaceutical compositions comprising the compounds of the invention and methods of using the compositions in the treatment of proliferative, inflammatory, infectious, neurological or cardiovascular diseases or disorders.

SUBSTITUTED HYDROXAMIC ACIDS AND USES THEREOF

PRIORITY CLAIM

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 61/377,238 filed August 26, 2010, incorporated by reference in its entirety, and U.S. Provisional Patent Application Serial No. 61/426,319, filed December 22, 2010, incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The invention relates to compounds and methods for the selective inhibition of HDAC6. The present invention relates to compounds useful as HDAC6 inhibitors. The invention also provides pharmaceutical compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various diseases.

BACKGROUND OF THE INVENTION

[0003] Histone deacetylase 6 (HDAC6) is a member of a family of amidohydrolases commonly referred as histone or lysine deacetylases (HDACs or KDACs) as they catalyze the removal of acetyl groups from the ε-amino group of lysine residues from proteins. The family includes 18 enzymes which can be divided in 3 main classes based on their sequence homology to yeast enzymes Rpd3 (Class I), Hda1 (Class II) and Sir2 (Class III). A fourth class was defined with the finding of a distinct mammalian enzyme - HDAC11 (reviewed in Yang, *et al., Nature Rev. Mol. Cell Biol.* **2008,** 9:206–218 and in Saunders and Verdin, *Oncogene* **2007**, 26(37):5489-5504). Biochemically, Class I (HDAC1, 2, 3, 8) and Class II (HDAC4, 5, 6, 7, 9, 10) and Class IV (HDAC11) are Zn^{2+}- dependent enzymes, while Class III (SIRT1-7) are dependent on nicotinamide adenine dinucleotide (NAD^+) for activity. Unlike all other HDACs, HDAC6 resides primarily in the cytosol. It has 2 functional catalytic domains and a carboxy-terminal Zn^{2+}-finger ubiquitin binding domain that binds ubiquitinated misfolded proteins (Kawaguchi *et al., Cell* **2003**, 115(6):727-738), ubiquitin (Boyaullt *et al., EMBO J.* **2006**, 25(14): 3357–3366), as well as ubiquitin-like FAT10 modifier (Kalveram *et al., J. Cell Sci.* **2008**, 121(24):4079-4088). Known substrates of HDAC6 include cytoskeletal proteins α-tubulin and cortactin; β-catenin which forms part of adherens junctions and anchors the actin cytoskeleton; the chaperone Hsp90; and the redox regulatory proteins peroxiredoxin (Prx) I and Prx II (reviewed in Boyault *et al., Oncogene* **2007**, 26(37):5468-5476; Matthias *et al., Cell Cycle* **2008**, 7(1):7-10; Li *et al., J Biol. Chem.* **2008**, 283(19):12686-12690; Parmigiani *et al., Proc. Natl. Acad. Sci. USA* **2009**, 105(28):9633-9638). Thus, HDAC6 mediates a wide range of cellular functions including microtubule-dependent trafficking and signaling, membrane remodeling and chemotactic motility, involvement in control of cellular adhesion, ubiquitin level sensing,

regulation of chaperone levels and activity, and responses to oxidative stress. All of these functions may be important in tumorigenesis, tumor growth and survival as well as metastasis (Simms-Waldrip *et al.*, *Mol. Genet. Metabolism* **2008**, 94(3):283-286; Rodriguez-Gonzalez *et al.*, *Cancer Res.* **2008**, 68(8):2557-2560; Kapoor, *Int. J. Cancer* **2009**, 124:509; Lee *et al.*, *Cancer Res.* **2008**, 68(18):7561-7569). Recent studies have shown HDAC6 to be important in autophagy, an alternative pathway for protein degradation that compensates for deficiencies in the activity of the ubiquitin proteasome system or expression of proteins prone to form aggregates and can be activated following treatment with a proteasome inhibitor (Kawaguchi *et al.*, *Cell* **2003**, 115(6):727-738; Iwata *et al.*, *J. Biol. Chem.* **2005**, 280(48): 40282-40292; Ding *et al.*, *Am. J. Pathol.* **2007**, 171:513-524, Pandey *et al.*, *Nature* **2007**, 447(7146):860-864). Although the molecular mechanistic details are not completely understood, HDAC6 binds ubiquitinated or ubiquitin-like conjugated misfolded proteins which would otherwise induce proteotoxic stress and then serves as an adaptor protein to traffic the ubiquitinated cargo to the microtubule organizing center using the microtubule network via its known association with dynein motor protein. The resulting perinuclear aggregates, known as aggresomes, are then degraded by fusion with lysosomes in an HDAC6- and cortactin-dependent process which induces remodeling of the actin cytoskeleton proximal to aggresomes (Lee *et al.*, *EMBO J.* **2010**, 29:969-980). In addition, HDAC6 regulates a variety of biological processes dependent on its association with the microtubular network including cellular adhesion (Tran *et al.*, *J. Cell Sci.* **2007**, 120(8):1469-1479) and migration (Zhang *et al.*, *Mol. Cell* **2007**, 27(2):197-213; reviewed in Valenzuela-Fernandez *et al.*, *Trends Cell. Biol.* **2008**, 18(6):291-297), epithelial to mesenchymal transition (Shan *et al.*, *J. Biol. Chem.* **2008**, 283(30):21065-21073), resistance to anoikis (Lee *et al.*, *Cancer Res.* **2008**, 68(18):7561-7569), epithelial growth factor-mediated Wnt signaling via β-catenin deacetylation (Li *et al.*, *J. Biol. Chem.* **2008**, 283(19):12686-12690) and epithelial growth factor receptor stabilization by endocytic trafficking (Lissanu Deribe *et al.*, *Sci. Signal.* **2009**, 2(102): ra84; Gao *et al.*, *J. Biol. Chem.* **2010**, 285:11219-11226); all events that promote oncogenesis and metastasis (Lee *et al.*, *Cancer Res.* **2008**, 68(18):7561-7569). HDAC6 activity is known to be upregulated by Aurora A kinase in cilia formation (Pugacheva *et al.*, *Cell* **2007**, 129(7):1351-1363) and indirectly by farnesyl transferase with which HDAC6 forms a complex with microtubules (Zhou *et al.*, *J. Biol. Chem.* **2009**, 284(15): 9648-9655). Also, HDAC6 is negatively regulated by tau protein (Perez *et al.*, *J. Neurochem.* **2009**, 109(6):1756-1766).

[0004] Diseases in which selective HDAC6 inhibition could have a potential benefit include cancer (reviewed in Simms-Waldrip *et al.*, *Mol. Genet. Metabolism* **2008**, 94(3):283-286 and Rodriguez-Gonzalez *et al.*, *Cancer Res.* **2008**, 68(8):2557-2560), specifically: multiple myeloma (Hideshima *et al.*, *Proc. Natl. Acad. Sci. USA* **2005**, 102(24):8567-8572); lung cancer (Kamemura *et al.*, *Biochem. Biophys. Res. Commun.* **2008**, 374(1):84-89); ovarian cancer (Bazzaro *et al.*, *Clin. Cancer Res.* **2008**, 14(22):7340-

7347); breast cancer (Lee *et al.*, *Cancer Res.* **2008**, 68(18):7561-7569); prostate cancer (Mellado *et al.*, *Clin. Trans. Onco.* **2009**, 11(1):5-10); pancreatic cancer (Nawrocki *et al.*, *Cancer Res.* **2006**, 66(7):3773-3781); renal cancer (Cha *et al.*, *Clin. Cancer Res.* **2009**, 15(3):840-850); and leukemias such as acute myeloid leukemia (AML) (Fiskus *et al.*, *Blood* **2008**, 112(7):2896-2905) and acute lymphoblastic leukemia (ALL) (Rodriguez-Gonzalez *et al.*, *Blood* **2008**, 112(11): Abstract 1923).

[0005] Inhibition of HDAC6 may also have a role in cardiovascular disease, i.e. cardiovascular stress, including pressure overload, chronic ischemia, and infarction-reperfusion injury (Tannous *et al.*, *Circulation* **2008**, 117(24):3070-3078); bacterial infection, including those caused by uropathogenic *Escherichia coli* (Dhakal and Mulve, *J. Biol. Chem.* **2008**, 284(1):446-454); neurological diseases caused by accumulation of intracellular protein aggregates such as Huntington's disease (reviewed in Kazantsev *et al.*, *Nat. Rev. Drug Disc.* **2008**, 7(10):854-868; see also Dompierre *et al.*, *J. Neurosci.* **2007**, 27(13):3571-3583; Kozikowski *et al.*, *J. Med. Chem.* **2007**, 50:3054–3061) or central nervous system trauma caused by tissue injury, oxidative-stress induced neuronal or axomal degeneration (Rivieccio *et al.*, *Proc. Natl. Acad. Sci. USA* **2009**, 106(46):19599-195604); and inflammation, including reduction of pro-inflammatory cytokine IL-1β (Carta *et al.*, *Blood* **2006**, 108(5):1618-1626), increased expression of the FOXP3 transcription factor, which induces immunosuppressive function of regulatory T-cells resulting in benefits in chronic diseases such as rheumatoid arthritis, psoriasis, multiple sclerosis, lupus and organ transplant rejection (reviewed in Wang *et al.*, *Nat. Rev. Drug Disc.* **2009**, 8(12):969-981).

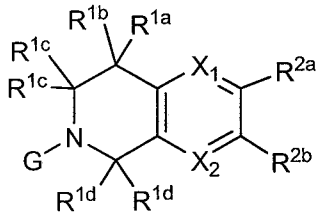
[0006] Given the complex function of HDAC6, selective inhibitors could have potential utility when used alone or in combination with other chemotherapeutics such as microtubule destabilizing agents (Zhou *et al.*, *J. Biol. Chem.* **2009**, 284(15): 9648-9655); Hsp90 inhibitors (Rao *et al.*, *Blood* **2008**, 112(5)1886-1893); inhibitors of Hsp90 client proteins, including receptor tyrosine kinases such as Her-2 or VEGFR (Bhalla *et al.*, *J. Clin. Oncol.* **2006**, 24(18S): Abstract 1923; Park *et al.*, *Biochem. Biophys. Res. Commun.* **2008**, 368(2):318-322), and signaling kinases such as Bcr-Abl, Akt, mutant FLT-3, c-Raf, and MEK (Bhalla *et al.*, *J. Clin. Oncol.* **2006**, 24(18S): Abstract 1923; Kamemura *et al.*, *Biochem. Biophys. Res. Commun.* **2008**, 374(1):84-89); inhibitors of cell cycle kinases Aurora A and Aurora B (Pugacheva *et al.*, *Cell* **2007**, 129(7):1351-1363; Park *et al.*, *J. Mol. Med.* **2008**, 86(1):117–128; Cha *et al.*, *Clin. Cancer Res.* **2009**, 15(3):840-850); EGFR inhibitors (Lissanu Deribe *et al.*, *Sci. Signal.* **2009**, 2(102): ra84; Gao *et al.*, *J. Biol. Chem.* **2010**, 285:11219-11226) and proteasome inhibitors (Hideshima *et al.*, *Proc. Natl. Acad. Sci. USA* **2005**, 102(24):8567-8572) or other inhibitors of the ubiquitin proteasome system such as ubiquitin and ubiqutin-like activating (E1), conjugation (E2), ligase enzymes (E3, E4) and deubiquitinase enzymes (DUBs) as well as modulators of autophagy and protein homeostasis pathways. In addition, HDAC6 inhibitors could be combined with radiation therapy (Kim *et al.*, *Radiother. Oncol.* **2009**, 92(1):125-132.

[0007] Clearly, it would be beneficial to provide novel HDAC6 inhibitors that possess good therapeutic properties, especially for the treatment of proliferative diseases or disorders.

DETAILED DESCRIPTION OF THE INVENTION

1. General Description of Compounds of the Invention

[0008] The present invention provides compounds that are effective inhibitors of HDAC6. These compounds are useful for inhibiting HDAC6 activity *in vitro* and *in vivo*, and are especially useful for the treatment of various cell proliferative diseases or disorders. The compounds of the invention are represented by formula (*I*):



(*I*);

or a pharmaceutically acceptable salt thereof;

wherein:

one of X_1 and X_2 is CR^1 and the other is N; or both X_1 and X_2 are N;

one of R^{2a} and R^{2b} is R^1, and the other is -C(O)-NH-OH;

R^{1a} is hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl;

R^{1b} is hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl;

or R^{1a} and R^{1b} are taken together to form a 3 to 6 membered cycloaliphatic;

R^{1c} and R^{1d} are:

I) each occurrence of R^{1c} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl; and each occurrence of R^{1d} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl; or

II) two occurrences of R^{1c} are taken together to form =O; and each occurrence of R^{1d} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl; or

III) two occurrences of R^{1d} are taken together to form =O; and each occurrence of R^{1c} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl;

each occurrence of R^1 is independently hydrogen, chloro, fluoro, -O-C_{1-4} alkyl, cyano, hydroxy, C_{1-4} alkyl, or C_{1-4} fluoroalkyl;

G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, $-L_2-V_1-R^3$, $-L_2-V_2-R^3$, $-V_1-L_1-V_2-R^3$, or $-L_1-R^3$;

L_1 is unsubstituted or substituted C_{1-3} alkylene chain;

L_2 is unsubstituted or substituted C_{2-3} alkylene chain;

V_1 is -C(O)-, -C(S)-, -C(O)-N(R^{4a})-, -C(O)-O-, -$S(O)_2$-, or -SO_2-N(R^{4a})-;

V_2 is -N(R^{4a})-, -N(R^{4a})-C(O)-, -N(R^{4a})-SO_2-, -SO_2-N(R^{4a})-, -SO_2-, -C(O)-, -C(O)-O-, -O-C(O)-, -O-, -S-, -N(R^{4a})-C(O)-N(R^{4a})-, -N(R^{4a})-C(O)-O-, -O-C(O)-N(R^{4a})-, or -N(R^{4a})-SO_2-N(R^{4a})-;

R^3 is unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each occurrence of R^{4a} is independently hydrogen, or unsubstituted or substituted C_{1-4} aliphatic.

2. Compounds and Definitions

[0009] Compounds of this invention include those described generally for formula (*I*) above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated.

[0010] As described herein, compounds of the invention may be optionally substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, means that a hydrogen radical of the designated moiety is replaced with the radical of a specified substituent, provided that the substitution results in a stable or chemically feasible compound. The term "substitutable", when used in reference to a designated atom, means that attached to the atom is a hydrogen radical, which hydrogen atom can be replaced with the radical of a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a 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.

[0011] A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature from about –80 °C to about +40 °C, in the absence of moisture or other chemically reactive conditions, for at least a week, or a compound which maintains its integrity long enough to be useful for therapeutic or prophylactic administration to a patient.

[0012] The phrase "one or more substituents", as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites, provided that the above conditions of stability and chemical feasibility are met.

[0013] As used herein, the term "independently selected" means that the same or different values may be selected for multiple instances of a given variable in a single compound.

[0014] As used herein, the term "aromatic" includes aryl and heteroaryl groups as described generally below and herein.

[0015] The term "aliphatic" or "aliphatic group", as used herein, means an optionally substituted straight-chain or branched C_{1-12} hydrocarbon. For example, suitable aliphatic groups include optionally substituted linear, or branched alkyl, alkenyl, alkynyl groups and hybrids thereof. Unless otherwise specified, in various embodiments, aliphatic groups have 1–12, 1–10, 1–8, 1–6, 1–4, 1–3, or 1-2 carbon atoms.

[0016] The term "alkyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having 1–12, 1–10, 1–8, 1–6, 1–4, 1–3, or 1-2 carbon atoms.

[0017] The term "alkenyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one double bond and having 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms.

[0018] The term "alkynyl", used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one triple bond and having 2-12, 2-10, 2-8, 2-6, 2-4, or 2-3 carbon atoms.

[0019] The terms "cycloaliphatic", "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic", used alone or as part of a larger moiety, refer to an optionally substituted saturated or partially unsaturated cyclic aliphatic ring system having from 3 to about 14 ring carbon atoms. In some embodiments, the cycloaliphatic group is an optionally substituted monocyclic hydrocarbon having 3-10, 3-8 or 3-6 ring carbon atoms. Cycloaliphatic groups include, without limitation, optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl,

cyclooctenyl, or cyclooctadienyl. The terms "cycloaliphatic", "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic" also include optionally substituted bridged or fused bicyclic rings having 6-12, 6-10, or 6-8 ring carbon atoms, wherein any individual ring in the bicyclic system has 3-8 ring carbon atoms.

[0020] The term "cycloalkyl" refers to an optionally substituted saturated ring system of about 3 to about 10 ring carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0021] The term "cycloalkenyl" refers to an optionally substituted non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and having about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[0022] The terms "haloaliphatic", "haloalkyl", "haloalkenyl" and "haloalkoxy" refer to an aliphatic, alkyl, alkenyl or alkoxy group, as the case may be, which is substituted with one or more halogen atoms. As used herein, the term "halogen" or "halo" means F, Cl, Br, or I. The term "fluoroaliphatic" refers to a haloaliphatic wherein the halogen is fluoro, including perfluorinated aliphatic groups. Examples of fluoroaliphatic groups include, without limitation, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1,1,2-trifluoroethyl, 1,2,2-trifluoroethyl, and pentafluoroethyl.

[0023] The term "heteroatom" refers to one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR+ (as in N-substituted pyrrolidinyl)).

[0024] The terms "aryl" and "ar-", used alone or as part of a larger moiety, e.g., "aralkyl", "aralkoxy", or "aryloxyalkyl", refer to an optionally substituted C_{6-14}aromatic hydrocarbon moiety comprising one to three aromatic rings. Preferably, the aryl group is a C_{6-10}aryl group. Aryl groups include, without limitation, optionally substituted phenyl, naphthyl, or anthracenyl. The terms "aryl" and "ar-", as used herein, also include groups in which an aryl ring is fused to one or more cycloaliphatic rings to form an optionally substituted cyclic structure such as a tetrahydronaphthyl, indenyl, or indanyl ring. The term "aryl" may be used interchangeably with the terms "aryl group", "aryl ring", and "aromatic ring".

[0025] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently attached to an alkyl group, either of which independently is optionally substituted. Preferably, the aralkyl group is C_{6-10}arylC_{1-6}alkyl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0026] 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 14 ring atoms, preferably 5, 6, 9, or 10 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. In some embodiments, the heteroaryl group has 5-10 ring atoms, having, in addition to carbon atoms, from one to five heteroatoms. A heteroaryl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. 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. For example, a nitrogen atom of a heteroaryl may be a basic nitrogen atom and may also be optionally oxidized to the corresponding N-oxide. When a heteroaryl is substituted by a hydroxy group, it also includes its corresponding tautomer. 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 heterocycloaliphatic rings. Nonlimiting examples of heteroaryl groups include thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, pteridinyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-b]-1,4-oxazin-3(4H)-one. 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.

[0027] As used herein, the terms "heterocycle", "heterocyclyl", "heterocyclic radical", and "heterocyclic ring" are used interchangeably and refer to a stable 4-10 membered ring, preferably a 3- to 8-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).

[0028] 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, tetrahydrothienyl, piperidinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and thiomorpholinyl. A heterocyclyl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably 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. Additionally, a heterocyclic ring also includes groups in which the heterocyclic ring is fused to one or more aryl rings.

[0029] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic (e.g., aryl or heteroaryl) moieties, as herein defined.

[0030] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_{n'}-$, 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. An optionally substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms is optionally replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group and also include those described in the specification herein. It will be appreciated that two substituents of the alkylene group may be taken together to form a ring system. In certain embodiments, two substituents can be taken together to form a 3-7-membered ring. The substituents can be on the same or different atoms.

[0031] An alkylene chain also can be optionally interrupted by a functional group. An alkylene chain is "interrupted" by a functional group when an internal methylene unit is interrupted by the functional group. Examples of suitable "interrupting functional groups" are described in the specification and claims herein.

[0032] For purposes of clarity, all bivalent groups described herein, including, *e.g.*, the alkylene chain linkers described above, are intended to be read from left to right, with a corresponding left-to-right reading of the formula or structure in which the variable appears.

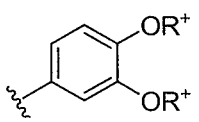
[0033] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents and thus may be "optionally substituted". In addition to the substituents defined above and herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group also include and are generally selected from -halo, $-NO_2$, -CN, $-R^+$, $-C(R^+)=C(R^+)_2$, $-C\equiv C-R^+$, $-OR^+$, $-SR^\circ$, $-S(O)R^\circ$, $-SO_2R^\circ$, $-SO_3R^+$, $-SO_2N(R^+)_2$, $-N(R^+)_2$, $-NR^+C(O)R^+$, $-NR^+C(S)R^+$, $-NR^+C(O)N(R^+)_2$, $-NR^+C(S)N(R^+)_2$, $-N(R^+)C(=NR^+)-N(R^+)_2$, $-N(R^+)C(=NR^+)-R^\circ$, $-NR^+CO_2R^+$, $-NR^+SO_2R^\circ$, $-NR^+SO_2N(R^+)^2$, $-O-C(O)R^+$, $-O-CO_2R^+$, $-OC(O)N(R^+)_2$, $-C(O)R^+$, $-C(S)R^\circ$, $-CO_2R^+$, $-C(O)-C(O)R^+$, $-C(O)N(R^+)_2$, $-C(S)N(R^+)_2$, $-C(O)N(R^+)-OR^+$, $-C(O)N(R^+)C(=NR^+)-N(R^+)_2$, $-N(R^+)C(=NR^+)-N(R^+)-C(O)R^+$, $-C(=NR^+)-N(R^+)_2$, $-C(=NR^+)-OR^+$, $-N(R^+)-N(R^+)_2$, $-C(=NR^+)-N(R^+)-OR^+$, $-C(R^\circ)=N-OR^+$, $-P(O)(R^+)_2$, $-P(O)(OR^+)_2$, $-O-P(O)-OR^+$, and $-P(O)(NR^+)-N(R^+)_2$, wherein R^+, independently, is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, cycloaliphatic, or heterocyclyl group, or two independent occurrences of R^+ are taken together with their intervening atom(s) to form an optionally substituted 5-7-

membered aryl, heteroaryl, cycloaliphatic, or heterocyclyl ring. Each R° is an optionally substituted aliphatic, aryl, heteroaryl, cycloaliphatic, or heterocyclyl group.

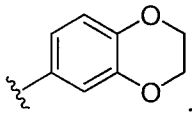
[0034] An aliphatic or heteroaliphatic group, or a non-aromatic carbycyclic or heterocyclic ring may contain one or more substituents and thus may be "optionally substituted". Unless otherwise defined above and herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic carbocyclic or heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, $=C(R^*)_2$, =N-$N(R^*)_2$, =N-OR*, =N-NHC(O)R*, =N-$NHCO_2R^\circ$ =N-$NHSO_2R^\circ$ or =N-R* where R° is defined above, and each R* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group.

[0035] In addition to the substituents defined above and herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring also include and are generally selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-C(O)OR^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-S(O)_2R^+$, $-S(O)_2N(R^+)_2$, $-C(S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-N(R^+)S(O)_2R^+$; wherein each R^+ is defined above. A ring nitrogen atom of a heteroaryl or non-aromatic heterocyclic ring also may be oxidized to form the corresponding N-hydroxy or N-oxide compound. A nonlimiting example of such a heteroaryl having an oxidized ring nitrogen atom is N-oxidopyridyl.

[0036] As detailed above, in some embodiments, two independent occurrences of R^+ (or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) to form a monocyclic or bicyclic ring selected from 3–13-membered cycloaliphatic, 3–12-membered heterocyclyl having 1–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6–10-membered aryl, or 5–10-membered heteroaryl having 1–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0037] Exemplary rings that are formed when two independent occurrences of R^+ (or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) include, but are not limited to the following: a) two independent occurrences of R^+ (or any other variable similarly defined in the specification or claims herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^+)_2$, where both occurrences of R^+ are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R^+ (or any other variable similarly defined in the specification or claims herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of OR^+ 

, these two occurrences of R^+ are taken together with the oxygen atoms to which they are bound to form a fused 6-

membered oxygen containing ring:  . It will be appreciated that a variety of other rings (e.g., spiro and bridged rings) can be formed when two independent occurrences of R+ (or any other variable similarly defined in the specification and claims herein) are taken together with their intervening atom(s) and that the examples detailed above are not intended to be limiting.

[0038] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a 13C- or 14C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0039] The terms "stereoisomer", "enantiomer", "diastereomer", "epimer", and "chiral center", are used herein in accordance with the meaning each is given in ordinary usage by those of ordinary skill in the art. Thus, stereoisomers are compounds that have the same atomic connectivity, but differ in the spatial arrangement of the atoms. Enantiomers are stereoisomers that have a mirror image relationship, that is, the stereochemical configuration at all corresponding chiral centers is opposite. Diastereomers are stereoisomers having more than one chiral center, which differ from one another in that the stereochemical configuration of at least one, but not all, of the corresponding chiral centers is opposite. Epimers are diastereomers that differ in stereochemical configuration at only one chiral center.

[0040] It is to be understood that, when a disclosed compound has at least one chiral center, the present invention encompasses one enantiomer of the compound, substantially free from the corresponding optical isomer, a racemic mixture of both optical isomers of the compound, and mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a mixture is enriched in one enantiomer relative to its optical isomer, the mixture contains, for example, an enantiomeric excess of at least 50%, 75%, 90%, 95%, 99%, or 99.5%.

[0041] The enantiomers of the present invention may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by

crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. Where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

[0042] When a disclosed compound has at least two chiral centers, the present invention encompasses a diastereomer substantially free of other diastereomers, an enantiomeric pair of diastereomers substantially free of other stereoisomers, mixtures of diastereomers, mixtures of enantiomeric pairs of diastereomers, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s), and mixtures of enantiomeric pairs of diastereomers in which one enantiomeric pair of diastereomers is enriched relative to the other stereoisomers. When a mixture is enriched in one diastereomer or enantiomeric pair of diastereomers pairs relative to the other stereoisomers, the mixture is enriched with the depicted or referenced diastereomer or enantiomeric pair of diastereomers relative to other stereoisomers for the compound, for example, by a molar excess of at least 50%, 75%, 90%, 95%, 99%, or 99.5%.

[0043] As used herein, the term "diastereomeric ratio" refers to the ratio between diastereomers which differ in the stereochemical configuration at one chiral center, relative to a second chiral center in the same molecule. By way of example, a chemical structure with two chiral centers provides four possible stereoisomers: *R*R*, *R*S*, *S*R*, and *S*S*, wherein the asterisk denotes the corresponding chiral center in each stereoisomer. The diastereomeric ratio for such a mixture of stereoisomers is the ratio of one diastereomer and its enantiomer to the other diastereomer and its enantiomer = (*R*R* + *S*S*) : (*R*S* + *S*R*).

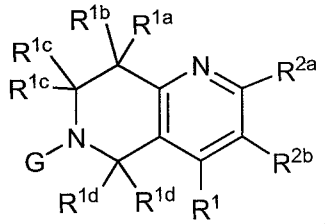
[0044] One of ordinary skill in the art will recognize that additional stereoisomers are possible when the molecule has more than two chiral centers. For purposes of the present invention, the term "diastereomeric ratio" has identical meaning in reference to compounds with multiple chiral centers as it does in reference to compounds having two chiral centers. Thus, the term "diastereomeric ratio" refers to the ratio of all compounds having *R*R* or *S*S* configuration at the specified chiral centers to all compounds having *R*S* or *S*R* configuration at the specified chiral centers. For convenience, this ratio is referred to herein as the diastereomeric ratio at the asterisked carbon, relative to the second specified chiral center.

[0045] The diastereomeric ratio can be measured by any analytical method suitable for distinguishing between diastereomeric compounds having different relative stereochemical configurations at the specified chiral centers. Such methods include, without limitation, nuclear magnetic resonance (NMR), gas chromatography (GC), and high performance liquid chromatography (HPLC) methods.

[0046] The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. Specific procedures for chromatographically separating diastereomeric pairs of precursors used in the preparation of compounds disclosed herein are provided the examples herein.

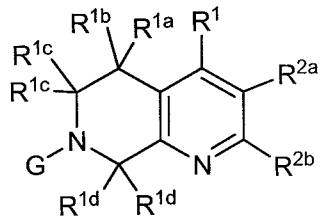
3. Description of Exemplary Compounds

[0047] In some embodiments, the compound of formula (*I*) is represented by:



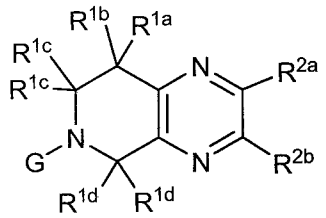
(*I-a*)

,



(*I-b*)

, or

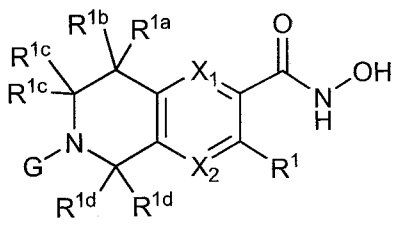


(*I-c*)

;

wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1}, R^{2a}, R^{2b}, and G have the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*I-a*), wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1}, R^{2a}, R^{2b}, and G have the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*I-b*), wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1}, R^{2a}, R^{2b}, and G have the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*I-c*), wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1}, R^{2a}, R^{2b}, and G have the values described herein.

[0048] In some embodiments, the compound of formula (*I*) is represented by formula (*II-a*) or (*II-b*):



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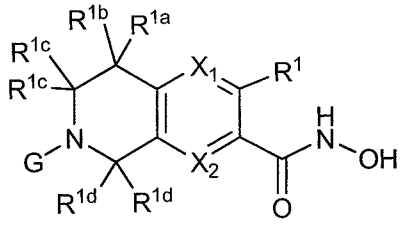
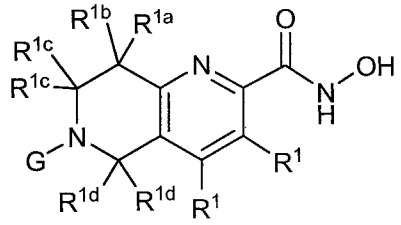


;

(*II-a*) (*II-b*)

wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^1, X_1, X_2, and G have the values described herein.

[0049] In some embodiments, the compound of formula (*I*) is represented by formula (*II-a-i*)-(*II-b-iii*):



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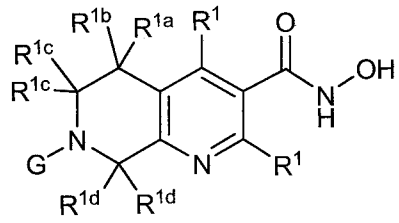
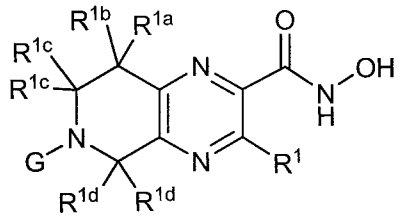


,

(*II-a-i*) (*II-a-ii*)



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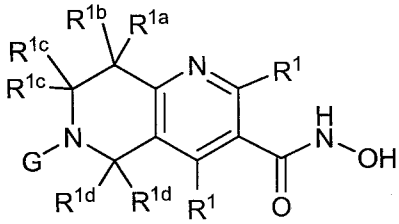
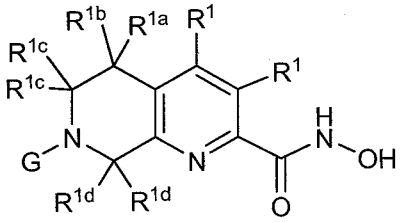


,

(*II-a-iii*) (*II-b-i*)



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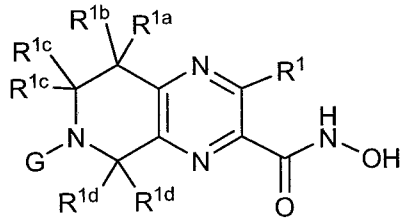
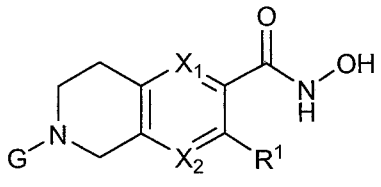


;

(*II-b-ii*) (*II-b-iii*)

wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^1, and G have the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*II-a-i*), wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^1, and G have the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*II-a-ii*), wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^1, and G have the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*II-b-i*), wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^1, and G have the values described herein.

[0050] In some embodiments, the compound of formula (*I*) is represented by formula (*III-a*) or (*III-b*):



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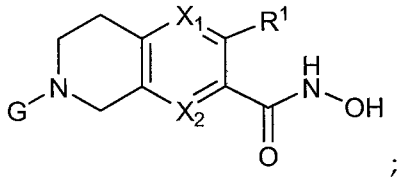
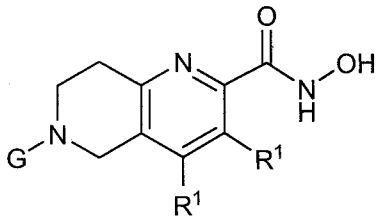


;

(*III-a*) (*III-b*)

wherein R^1, X_1, X_2, and G have the values described herein.

[0051] In some embodiments, the compound of formula (*I*) is represented by formula (*III-a-i*)-(*III-b-iii*):



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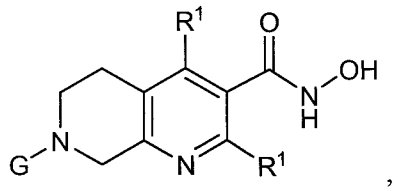
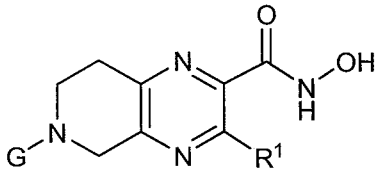


,

(*III-a-i*) (*III-a-ii*)



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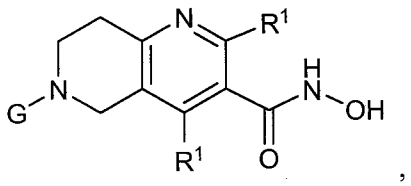
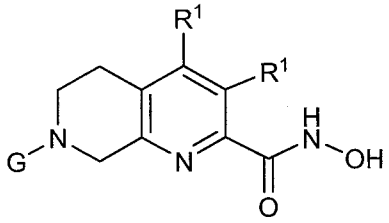


,

(*III-a-iii*) (*III-b-i*)



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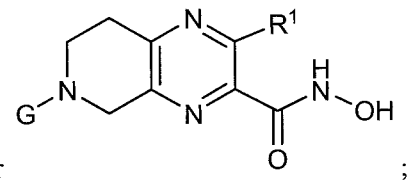
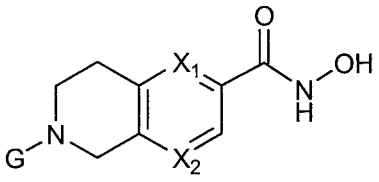


;

(*III-b-ii*) (*III-b-iii*)

wherein R^1 and G have the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*III-a-i*), wherein R^1 and G have the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*III-a-ii*), wherein R^1 and G have the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*III-b-i*), wherein R^1 and G have the values described herein.

[0052] In some embodiments, the compound of formula (*I*) is represented by formula (*IV-a*) or (*IV-b*):



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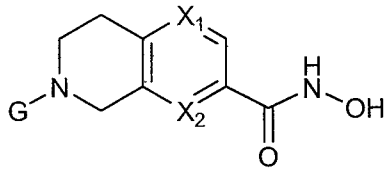
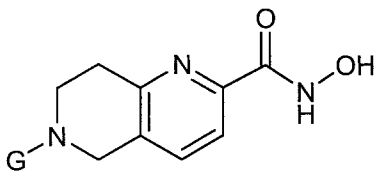


;

(*IV-a*) (*IV-b*)

wherein X_1, X_2, and G have the values described herein.

[0053] In some embodiments, the compound of formula (*I*) is represented by formula (*IV-a-i*)-(*IV-b-iii*):



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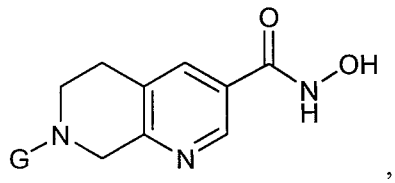
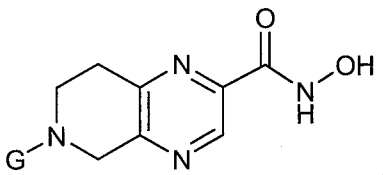


,

(*IV-a-i*) (*IV-a-ii*)



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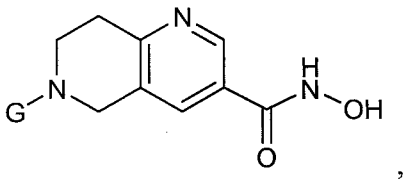
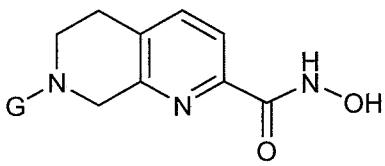
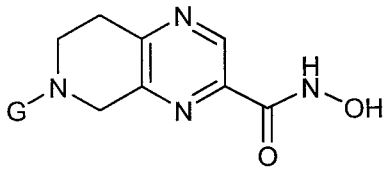


,

(*IV-a-iii*) (*IV-b-i*)



, or



;

(*IV-b-ii*) (*IV-b-iii*)

wherein G has the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*IV-a-i*), wherein G has the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*IV-a-ii*), wherein G has the values described herein. In certain embodiments, the compound of formula (*I*) is represented by formula (*IV-b-i*), wherein G has the values described herein.

[0054] The values described below for each variable are with respect to any of formulas (*I*), (*II*), (*III*), (*IV*), or their sub-formulas as described above.

[0055] The variable R^{1a} is hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl. In some embodiments, R^{1a} is hydrogen, fluoro, methyl, or trifluoromethyl. In certain embodiments, R^{1a} is hydrogen, fluoro, or methyl. In certain embodiments, R^{1a} is hydrogen.

[0056] The variable R^{1b} is hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl. In some embodiments, R^{1b} is hydrogen, fluoro, methyl, or trifluoromethyl. In certain embodiments, R^{1b} is hydrogen, fluoro, or methyl. In certain embodiments, R^{1b} is hydrogen.

[0057] In some embodiments, R^{1a} and R^{1b} are taken together to form a 3-6 membered cycloaliphatic ring. In some embodiments, R^{1a} and R^{1b} are taken together to form cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In certain embodiments, R^{1a} and R^{1b} are taken together to form cyclopropyl.

[0058] In some embodiments, each occurrence of R^{1c} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl; and each occurrence of R^{1d} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl. In some embodiments, each occurrence of R^{1c} is hydrogen, fluoro, methyl, or trifluoromethyl. In some embodiments, each occurrence of R^{1c} is hydrogen, fluoro, or methyl. In certain embodiments, each occurrence of R^{1c} is hydrogen. In some embodiments, each occurrence of R^{1d} is hydrogen, fluoro, methyl, or trifluoromethyl. In some embodiments, each occurrence of R^{1d} is hydrogen, fluoro, or methyl. In certain embodiments, each occurrence of R^{1d} is hydrogen.

[0059] In some embodiments, two occurrences of R^{1c} are taken together to form =O; and each occurrence of R^{1d} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl. In some embodiments, two occurrences of R^{1c} are taken together to form =O; and each occurrence of R^{1d} is independently hydrogen, fluoro, methyl, or trifluoromethyl. In some embodiments, two occurrences of R^{1c} are taken together to form =O; and each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl. In some embodiments, two occurrences of R^{1c} are taken together to form =O; and each occurrence of R^{1d} is hydrogen.

[0060] In some embodiments, two occurrences of R^{1d} are taken together to form =O; and each occurrence of R^{1c} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl. In some embodiments, two occurrences of R^{1d} are taken together to form =O; and each occurrence of R^{1c} is independently hydrogen, fluoro, methyl, or trifluoromethyl. In some embodiments, two occurrences of R^{1d} are taken together to form =O; and each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl. In some embodiments, two occurrences of R^{1d} are taken together to form =O; and each occurrence of R^{1c} is hydrogen.

[0061] Each occurrence of the variable R^1 is independently hydrogen, chloro, fluoro, -O-C_{1-4} alkyl, cyano, hydroxy, C_{1-4} alkyl, or C_{1-4} fluoroalkyl. In some embodiments, each occurrence of R^1 is

independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl. In certain embodiments, each occurrence of R^1 is independently hydrogen, fluoro, or methyl. In certain embodiments, each occurrence of R^1 is hydrogen.

[0062] One of the variables X_1 and X_2 is CR^1 and the other is N; or both X_1 and X_2 are N, wherein R^1 has the values described herein. In some embodiments, X_1 is CR^1 and X_2 is N, wherein R^1 has the values described herein. In some embodiments, X_1 is N and X_2 is CR^1, wherein R^1 has the values described herein. In some embodiments, X_1 is N and X_2 is N.

[0063] One of the variable R^{2a} and R^{2b} is R^1, and the other is -C(O)-NH-OH, wherein R^1 has the values described herein. In some embodiments, R^{2a} is R^1 and R^{2b} is -C(O)-NH-OH, wherein R^1 has the values described herein. In some embodiments, R^{2b} is R^1 and R^{2a} is -C(O)-NH-OH, wherein R^1 has the values described herein.

[0064] The variable G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, $-L_2-V_1-R^3$, $-L_2-V_2-R^3$, $-V_1-L_1-V_2-R^3$, or $-L_1-R^3$, wherein L_1, V_1, L_2, V_2, and R^3 have the values described herein. In some embodiments, G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, or $-L_1-R^3$, wherein L_1, V_1, and R^3 have the values described herein. In some embodiments, G is $-V_1-R^3$, $-V_1-L_1-R^3$, or $-L_1-R^3$, wherein L_1, V_1, and R^3 have the values described herein. In certain embodiments, G is $-V_1-R^3$, wherein V_1 and R^3 have the values described herein. In certain embodiments, G is $-L_1-R^3$, wherein L_1 and R^3 have the values described herein. In certain embodiments, G is $-V_1-L_1-R^3$, wherein R^3 has the values described herein.

[0065] The variable L_1 is an unsubstituted or substituted C_{1-3} alkylene chain. In some embodiments, L_1 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CR^A=CR^A-$, or $-C\equiv C-$. In some embodiments, L_1 is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$. In certain embodiments, L_1 is $-CH_2-$. In certain embodiments, L_1 is $-CH_2CH_2-$.

[0066] The variable L_2 is an unsubstituted or substituted C_{2-3} alkylene chain. In some embodiments, L_2 is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$. In certain embodiments, L_2 is $-CH_2CH_2-$. In certain embodiments, L_2 is $-CH_2CH_2CH_2-$.

[0067] Each occurrence of the variable R^A is independently hydrogen, fluoro, or unsubstituted or substituted C_{1-4} aliphatic. In some embodiments, each occurrence of R^A is independently hydrogen, fluoro or methyl. In certain embodiments, each occurrence of R^A is hydrogen.

[0068] The variable V_1 is -C(O)-, -C(S)-, $-C(O)-N(R^{4a})-$, -C(O)-O-, $-S(O)_2-$, or $-SO_2-N(R^{4a})-$; wherein R^{4a} has the values described herein. In some embodiments, V_1 is -C(O)-, -C(S)-, -C(O)-NH-, -C(O)-O-, $-S(O)_2-$, or $-SO_2-NH-$. In certain embodiments, V_1 is -C(O)-, $-C(O)-N(R^{4a})-$, or $-S(O)_2-$ wherein R^{4a} has the values described herein. In certain embodiments, V_1 is -C(O)-, -C(O)-NH-, or $-S(O)_2$.

[0069] The variable V_2 is $-N(R^{4a})-$, $-N(R^{4a})-C(O)-$, $-N(R^{4a})-SO_2-$, $-SO_2-N(R^{4a})-$, $-SO_2-$, -C(O)-,

-C(O)-O-, -O-C(O)-, -O-, -S-, -N(R^{4a})-C(O)-N(R^{4a})-, -N(R^{4a})-C(O)-O-, -O-C(O)-N(R^{4a})-, or -N(R^{4a})-SO_2-N(R^{4a})-, wherein R^{4a} has the values described herein. In some embodiments, V_2 is -N(R^{4a})-, -N(R^{4a})-C(O)-, -N(R^{4a})-SO_2-, -O-, -S-, -N(R^{4a})-C(O)-N(R^{4a})-, -N(R^{4a})-C(O)-O-, -O-C(O)-N(R^{4a})-, or -N(R^{4a})-SO_2-N(R^{4a})-, wherein R^{4a} has the values described herein. In some embodiments, V_2 is -N(R^{4a})-, -N(R^{4a})-C(O)-, -N(R^{4a})-SO_2-, -SO_2-N(R^{4a})-, -O-, or -S-, wherein R^{4a} has the values described herein. In certain embodiments, V_2 is -NH-, -NH-C(O)-, -NH-SO_2-, -SO_2-NH-, -O-, or -S-. In certain embodiments, V_2 is -N(R^{4a})-, -O-, or -S-, wherein R^{4a} has the values described herein. In certain embodiments, V_2 is -NH-, -O-, or -S-.

[0070] Each occurrence of R^{4a} is independently hydrogen, or unsubstituted or substituted C_{1-4} aliphatic. In certain embodiments, each occurrence of R^{4a} is hydrogen.

[0071] The variable R^3 is unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0072] In some embodiments, R^3 is unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein:

each substitutable carbon chain atom in R^3 is unsubstituted or substituted with 1-2 occurrences of $-R^{5dd}$;

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with =O, $=C(R^5)_2$, or $-R^{5aa}$;

each substitutable unsaturated ring carbon atom in R^3 is unsubstituted or is substituted with $-R^{5a}$;

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$;

wherein R^{5dd}, R^5, R^{5a}, R^{5aa}, and R^{9b} have the values described herein.

[0073] In some embodiments, R^3 is unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or

substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein:

each substitutable carbon chain atom in R^3 is unsubstituted or substituted with 1-2 occurrences of $-R^{5dd}$;

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5aa}$;

each substitutable unsaturated ring carbon atom in R^3 is unsubstituted or is substituted with $-R^{5a}$;

the total number of R^{5a} and R^{5aa} substituents is p; and

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$;

wherein R^{5dd}, R^{5a}, R^{9b} and p have the values described herein.

[0074] Each occurrence of the variable R^{5dd} is independently fluoro, hydroxy, -O(C_{1-6} alkyl), cyano, -N(R^4)$_2$, -C(O)(C_{1-6} alkyl), -CO_2H, -C(O)NH_2, -C(O)NH(C_{1-6} alkyl), -C(O)N(C_{1-6} alkyl)$_2$, -NHC(O)C_{1-6} alkyl, -NHC(O)OC_{1-6} alkyl, -NHC(O)NHC_{1-6} alkyl, or -NHS(O)$_2C_{1-6}$ alkyl, wherein R^4 has the values described herein. In some embodiments, each occurrence of R^{5dd} is independently fluoro, hydroxy, methoxy, ethoxy, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, or -C(O)NHCH_3.

[0075] Each occurrence of the variable R^{9b} is independently -C(O)R^6, -C(O)N(R^4)$_2$, -CO_2R^6, -SO_2R^6, -SO_2N(R^4)$_2$, unsubstituted C_{3-10} cycloaliphatic, C_{3-10} cycloaliphatic substituted with 1-2 independent occurrences of R^7or R^8, unsubstituted C_{1-6} aliphatic, or C_{1-6} aliphatic substituted with 1-2 independent occurrences of R^7or R^8, wherein R^7 and R^8 have the values described herein. In some embodiments, each occurrence of R^{9b} is independently unsubstituted -C(O)-C_{1-6} aliphatic, unsubstituted -C(O)-C_{3-10} cycloaliphatic, or unsubstituted C_{1-6} aliphatic. In some embodiments, each occurrence of R^{9b} is unsubstituted C_{1-6} aliphatic. In certain embodiments, each occurrence of R^{9b} is independently methyl, ethyl, isopropyl, isobutyl, n-propyl, n-butyl, tert-butyl, -C(O)-methyl, -C(O)-ethyl, -C(O)-cyclopropyl, -C(O)-tert-butyl, -C(O)-isopropyl, or -C(O)-cyclobutyl. In certain embodiments, each occurrence of R^{9b} is independently methyl, ethyl, isopropyl, isobutyl, n-propyl, n-butyl, or tert-butyl.

[0076] Each occurrence of the variable R^4 is independently hydrogen, unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two R^4 on the same nitrogen atom, taken together with the nitrogen atom, form an unsubstituted or substituted 5- to

6-membered heteroaryl or an unsubstituted or substituted 4- to 8-membered heterocyclyl having, in addition to the nitrogen atom, 0-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur.

[0077] Each occurrence of the variable R^5 is independently hydrogen, unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0078] Each occurrence of the variable R^6 is independently unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0079] Each occurrence of the variable R^7 is independently unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0080] Each occurrence of the variable R^8 is independently chloro, fluoro, -OH, -O(C_{1-6} alkyl), -CN, -N(R^4)$_2$, -C(O)(C_{1-6} alkyl), -CO_2H, -CO_2(C_{1-6} alkyl), -C(O)NH_2, -C(O)NH(C_{1-6} alkyl), or -C(O)N(C_{1-6} alkyl)$_2$, wherein R^4 has the values described herein.

[0081] Each occurrence of the variable R^{5a} is independently halogen, -NO_2, -CN, -C(R^5)=C(R^5)$_2$, -C≡C-R^5, -OR^5, -SR^6, -S(O)R^6, -SO_2R^6, -SO_2N(R^4)$_2$, -N(R^4)$_2$, -NR^4C(O)R^6, -NR^4C(O)N(R^4)$_2$, -N$R^4$$CO_2R^6$, -OC(O)N($R^4$)$_2$, -C(O)$R^6$, -C(O)N($R^4$)$_2$, -N($R^4$)$SO_2R^6$, -N($R^4$)$SO_2$N($R^4$)$_2$, unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two adjacent R^{5a}, taken together with the intervening ring atoms, form an unsubstituted or substituted fused 5-10 membered aromatic ring or an unsubstituted or substituted 4-10 membered non-aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein R^5, R^6, and R^4 have the values described herein.

[0082] In some embodiments, each occurrence of R^{5a} is independently halogen, cyano, nitro, hydroxy, unsubstituted C_{1-6} aliphatic, C_{1-6} aliphatic substituted with 1-2 independent occurrences of R^7or R^8, unsubstituted –O-C_{1-6} alkyl, -O-C_{1-6} alkyl substituted with 1-2 independent occurrences of R^7or R^8, C_{1-6} fluoroalkyl, -O-C_{1-6} fluoroalkyl, -NHC(O)R^6, -C(O)NH(R^4), -NHC(O)O-C_{1-6} alkyl,

-NHC(O)NHC$_{1-6}$ alkyl, -NHS(O)$_2$C$_{1-6}$ alkyl, -NHC$_{1-6}$ alkyl, -N(C$_{1-6}$ alkyl)$_2$, 3-10-membered cycloaliphatic substituted with 0-2 occurrences of –R^{7a}, 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with 0-2 occurrences of –R^{7a}, 6-10-membered aryl substituted with 0-2 occurrences of –R^{7a}, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with 0-2 occurrences of –R^{7a}, wherein R^4, R^5, R^{7a}, R^7, and R^8 have the values described herein.

[0083] In certain embodiments, each occurrence of R^{5a} is independently chloro, fluoro, hydroxy, methoxy, ethoxy, cyano, trifluoromethyl, methyl, ethyl, isopropyl, -NHC(O)-tert-butyl, -NHC(O)-cyclopropyl, -NHC(O)R^{10}, -C(O)NHR^{10}, -CH$_2$-N(R^4)$_2$, or -NHSO$_2$CH$_3$, wherein R^{10} has the values described herein.

[0084] Each occurrence of the variable R^{10} is unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, each occurrence of R^{10} is unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein if substituted R^{10} is substituted with 0-2 occurrences of –R^{7aa}, wherein R^{7aa} has the values described herein. In some embodiments, each occurrence of R^{10} is pyrrolidinyl, piperidinyl, pyrrolinyl, piperazinyl, or morpholinyl, wherein each of the foregoing groups is unsubstituted or substituted with 0-1 occurrence of R^{7aa}, wherein R^{7aa} has the values described herein.

[0085] Each occurrence of the variable R^{5aa} is independently chloro, fluoro, hydroxy, unsubstituted or substituted C$_{1-6}$ aliphatic, -O(C$_{1-6}$ alkyl), -C$_{1-6}$ fluoroalkyl, -O-C$_{1-6}$ fluoroalkyl, cyano, -N(R^4)$_2$, -C(O)(C$_{1-6}$ alkyl), -CO$_2$H, -C(O)NH$_2$, -C(O)NH(C$_{1-6}$ alkyl), -C(O)N(C$_{1-6}$ alkyl)$_2$, -NHC(O)C$_{1-6}$ alkyl, -NHC(O)OC$_{1-6}$ alkyl, -NHC(O)NHC$_{1-6}$ alkyl, -NHC(O)N(C$_{1-6}$ alkyl)$_2$, or -NHS(O)$_2$C$_{1-6}$ alkyl. In some embodiments, each occurrence of R^{5aa} is independently chloro, fluoro, hydroxy, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, -C(O)NH$_2$, -N(C$_{1-6}$ alkyl)$_2$, -NHC$_{1-6}$ alkyl, or –CO$_2$H. In certain embodiments, each occurrence of R^{5aa} is independently fluoro, methyl, ethyl, methoxy, ethoxy, -C(O)NH$_2$, -N(C$_{1-6}$ alkyl)$_2$, -NHC$_{1-6}$ alkyl, or –CO$_2$H.

[0086] Each occurrence of the variable R^{7a} is independently chloro, fluoro, C$_{1-6}$ aliphatic, C$_{1-6}$ fluoroalkyl, -O-C$_{1-6}$ alkyl, -O-C$_{1-6}$ fluoroalkyl, cyano, hydroxy, -CO$_2$H, -NHC(O)C$_{1-6}$ alkyl, -NHC$_{1-6}$ alkyl, -N(C$_{1-6}$ alkyl)$_2$, -C(O)NHC$_{1-6}$ alkyl, -C(O)N(C$_{1-6}$ alkyl)$_2$, -NHC(O)NHC$_{1-6}$ alkyl, -NHC(O)N(C$_{1-6}$ alkyl)$_2$, or -NHS(O)$_2$C$_{1-6}$ alkyl.

[0087] Each occurrence of the variable R^{7aa} is independently chloro, fluoro, hydroxy, unsubstituted or substituted C$_{1-6}$ aliphatic, -O(C$_{1-6}$ alkyl), -C$_{1-6}$ fluoroalkyl, -O-C$_{1-6}$ fluoroalkyl, cyano, -N(R^4)$_2$, -C(O)(C$_{1-6}$ alkyl), -CO$_2$H, -C(O)NH$_2$, -C(O)NH(C$_{1-6}$ alkyl), -C(O)N(C$_{1-6}$ alkyl)$_2$, -NHC(O)C$_{1-6}$ alkyl,

-NHC(O)OC$_{1-6}$ alkyl, -NHC(O)NHC$_{1-6}$ alkyl, -NHC(O)N(C$_{1-6}$ alkyl)$_2$, or -NHS(O)$_2$C$_{1-6}$ alkyl. In some embodiments, each occurrence of R^{7aa} is independently fluoro, hydroxy, methyl, ethyl, methoxy, trifluoromethyl, -C(O)NH$_2$, or –CO$_2$H.

[0088] The variable p is 1-4. In some embodiments, p is 1-3. In certain embodiments, p is 1-2. In certain embodiments, p is 1.

[0089] In some embodiments, R^3 is unsubstituted or substituted C$_{1-6}$ aliphatic. In some embodiments, each substitutable carbon chain atom in R^3 is unsubstituted or substituted with 1-2 occurrences of -R^{5dd}, wherein R^{5dd} has the values described herein. In certain embodiments, R^3 is methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, iso-butyl, pentyl, hexyl, butenyl, propenyl, pentenyl, or hexenyl, wherein each of the forementioned groups is unsubstituted or substituted. In certain embodiments, R^3 is methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, iso-butyl, pentyl, hexyl, butenyl, propenyl, pentenyl, or hexenyl, wherein each substitutable carbon chain atom in R^3 is unsubstituted or substituted with 1-2 occurrences of -R^{5dd}, wherein R^{5dd} has the values described herein.

[0090] In some embodiments, R^3 is unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0091] In certain embodiments, R^3 is unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with =O, =C(R^5)$_2$, or –R^{5aa};

each substitutable unsaturated ring carbon atom in R^3 is unsubstituted or is substituted with -R^{5a}; and

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with -R^{9b};

wherein R^5, R^{5a}, R^{5aa}, and R^{9b} have the values described herein.

[0092] In certain embodiments, R^3 is unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or

substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5aa}$;

each substitutable unsaturated ring carbon atom in R^3 is unsubstituted or is substituted with $-R^{5a}$;

the total number of R^{5a} and R^{5aa} substituents is p; and

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$;

wherein R^{5a}, R^{5aa}, R^{9b} and p have the values described herein.

[0093] In certain embodiments, R^3 is furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, phenyl, naphthyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolizinyl, imidazopyridyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzthiazolyl, benzothienyl, benzofuranyl, benzoxazolyl, benzodioxolyl, benzthiadiazolyl, 2,3-dihydrobenzofuranyl, 4H-furo[3,2-b]pyrrolyl, pyrazolopyrimidinyl, purinyl, quinolyl, isoquinolyl, tetrahydroquinolinyl, tetrahydronaphthyridinyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, indanyl, tetrahydroindazolyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, thiomorpholinyl, quinuclidinyl, phenanthridinyl, tetrahydronaphthyl, indolinyl, benzodioxanyl, chromanyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, bicycloheptanyl, azabicyclooctanyl, oxabicyclooctanyl, bicyclononyl, bicyclooctanyl, or adamantyl; wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with =O, $=C(R^5)_2$, or $-R^{5aa}$;

each substitutable unsaturated ring carbon atom in R^3 is unsubstituted or is substituted with $-R^{5a}$; and

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$;

wherein R^5, R^{5a}, R^{5aa}, and R^{9b} have the values described herein.

[0094] In certain embodiments, R^3 is furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, phenyl, naphthyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolizinyl, imidazopyridyl, indolyl, isoindolyl, indazolyl,

benzimidazolyl, benzthiazolyl, benzothienyl, benzofuranyl, benzoxazolyl, benzodioxolyl, benzthiadiazolyl, 2,3-dihydrobenzofuranyl, 4H-furo[3,2-b]pyrrolyl, pyrazolopyrimidinyl, purinyl, quinolyl, isoquinolyl, tetrahydroquinolinyl, tetrahydronaphthyridinyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, indanyl, tetrahydroindazolyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, thiomorpholinyl, quinuclidinyl, phenanthridinyl, tetrahydronaphthyl, indolinyl, benzodioxanyl, chromanyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, bicycloheptanyl, azabicyclooctanyl, oxabicyclooctanyl, bicyclononyl, bicyclooctanyl, or adamantyl; wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5aa}$;

each substitutable unsaturated ring carbon atom in R^3 is unsubstituted or is substituted with $-R^{5a}$;

the total number of R^{5a} and R^{5aa} substituents is p; and

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$;

wherein R^{5a}, R^{5aa}, R^{9b}, and p have the values described herein.

[0095] In certain embodiments, R^3 is furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, phenyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, or triazinyl; wherein:

each substitutable unsaturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5a}$;

each occurrence of R^{5a} is independently chloro, fluoro, hydroxy, methoxy, ethoxy, cyano, trifluoromethyl, methyl, ethyl, isopropyl, -NHC(O)-tert-butyl, -NHC(O)-cyclopropyl, $-NHC(O)R^{10}$, $-C(O)NHR^{10}$, $-CH_2-N(R^4)_2$, or $-NHSO_2CH_3$;

the total number of R^{5a} substituents is p;

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$; and

each occurrence of R^{9b} is independently methyl, ethyl, isopropyl, isobutyl, n-propyl, n-butyl, or tert-butyl;

wherein p and R^{10} have the values described herein.

[0096] In certain embodiments, R^3 is indolizinyl, imidazopyridyl, indolyl, indazolyl, benzimidazolyl, benzthiazolyl, benzothienyl, benzofuranyl, benzoxazolyl, benzthiadiazolyl, pyrazolopyrimidinyl, purinyl,

quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, naphthyl, or pteridinyl; wherein:

each substitutable unsaturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5a}$;

each occurrence of R^{5a} is independently chloro, fluoro, hydroxy, methoxy, ethoxy, cyano, trifluoromethyl, methyl, ethyl, isopropyl, -NHC(O)-tert-butyl, -NHC(O)-cyclopropyl, $-NHC(O)R^{10}$, $-C(O)NHR^{10}$, $-CH_2-N(R^4)_2$, or $-NHSO_2CH_3$;

the total number of R^{5a} substituents is p;

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$; and

each R^{9b} is independently methyl, ethyl, isopropyl, isobutyl, n-propyl, n-butyl, or tert-butyl;

wherein p and R^{10} have the values described herein.

[0097] In certain embodiments, R^3 is tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, oxazolidinyl, piperazinyl, dioxanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, thiomorpholinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, or cyclooctenyl; wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5aa}$;

each substitutable unsaturated ring carbon atom in R^3 is unsubstituted or is substituted with $-R^{5a}$;

the total number of R^{5a} and R^{5aa} substituents is p;

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$;

each occurrence of R^{5a} is independently chloro, fluoro, hydroxy, methoxy, ethoxy, cyano, trifluoromethyl, methyl, ethyl, isopropyl, -NHC(O)-tert-butyl, -NHC(O)-cyclopropyl, $-NHC(O)R^{10}$, $-C(O)NHR^{10}$, $-CH_2-N(R^4)_2$, or $-NHSO_2CH_3$;

each occurrence of R^{5aa} is independently chloro, fluoro, hydroxy, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluromethoxy, $-C(O)NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $-NHC_{1-6}$ alkyl, or $-CO_2H$; and

each R^{9b} is independently methyl, ethyl, isopropyl, isobutyl, n-propyl, n-butyl, tert-butyl, -C(O)-methyl, -C(O)-ethyl, -C(O)-cyclopropyl, -C(O)-tert-butyl, -C(O)-isopropyl, or -C(O)-cyclobutyl;

wherein R^{10} and p have the values described herein.

[0098] In certain embodiments, R^3 is pyrrolidinyl, piperidinyl, or piperazinyl; wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5aa}$;

the total number of R^{5aa} substituents is p; and

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$;

wherein R^{5aa}, p, and R^{9b} have the values described herein.

[0099] In certain embodiments, R^3 is pyrrolidinyl, piperidinyl, or piperazinyl; wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5aa}$;

the total number of R^{5aa} substituents is p;

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$;

each occurrence of R^{5aa} is independently chloro, fluoro, hydroxy, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluromethoxy, $-C(O)NH_2$, $-N(C_{1-6}\ alkyl)_2$, $-NHC_{1-6}$ alkyl, or $-CO_2H$;

each occurrence of R^{9b} is independently methyl, ethyl, isopropyl, isobutyl, n-propyl, n-butyl, tert-butyl, -C(O)-methyl, -C(O)-ethyl, -C(O)-cyclopropyl, -C(O)-tert-butyl, -C(O)-isopropyl, or -C(O)-cyclobutyl; and

p is 1-2.

[00100] In certain embodiments, R^3 is tetrahydroindazolyl, bicycloheptanyl, azabicyclooctanyl, oxabicyclooctanyl, bicyclononyl, bicyclooctanyl, adamantyl, isoindolyl, benzodioxolyl, 2,3-dihydrobenzofuranyl, 4H-furo[3,2-b]pyrrolyl, quinuclidinyl, tetrahydroquinolinyl, tetrahydronaphthyridinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, tetrahydronaphthyl, indolinyl, benzodioxanyl, chromanyl, tetrahydroindazolyl, or indanyl; wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5aa}$;

each substitutable unsaturated ring carbon atom in R^3 is unsubstituted or is substituted with $-R^{5a}$;

the total number of R^{5a} and R^{5aa} substituents is p;

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$;

each occurrence of R^{5a} is independently chloro, fluoro, hydroxy, methoxy, ethoxy, cyano, trifluoromethyl, methyl, ethyl, isopropyl, -NHC(O)-tert-butyl, -NHC(O)-cyclopropyl, $-NHC(O)R^{10}$,

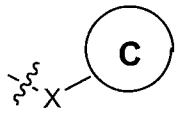
-C(O)NHR^{10}, -CH$_2$-N(R^4)$_2$, or -NHSO$_2$CH$_3$;

each occurrence of R^{5aa} is independently chloro, fluoro, hydroxy, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluromethoxy, -C(O)NH$_2$, -N(C$_{1-6}$ alkyl)$_2$, -NHC$_{1-6}$ alkyl, or –CO$_2$H; and

each R^{9b} is independently methyl, ethyl, isopropyl, isobutyl, n-propyl, n-butyl, tert-butyl, -C(O)-methyl, -C(O)-ethyl, -C(O)-cyclopropyl, -C(O)-tert-butyl, -C(O)-isopropyl, or -C(O)-cyclobutyl;

wherein R^{10} and p have the values described herein.

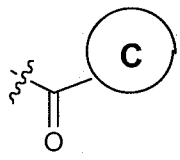
[00101] In some embodiments, G is:



;

wherein X and Ring C have the values described herein.

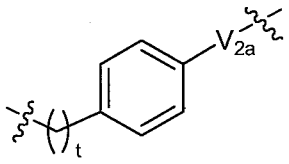
[00102] In certain embodiments, G is:



;

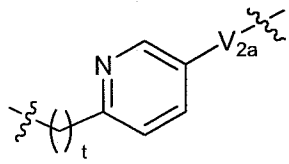
wherein Ring C has the values described herein.

[00103] The variable X is –C(O)- or –L$_{2a}$-R^{3aa}-V$_{2a}$-, wherein L$_{2a}$, R^{3aa}, and V$_{2a}$ have the values described herein. In some embodiments, X is –C(O)-. In some embodiments, X is –L$_{2a}$-R^{3aa}-V$_{2a}$-, wherein L$_{2a}$, R^{3aa}, and V$_{2a}$ have the values described herein. In some embodiments, X is –C(O)-,



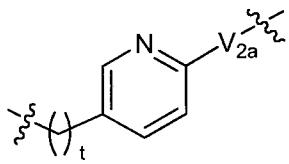
,

X-a



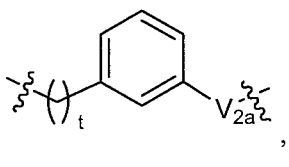
,

X-b



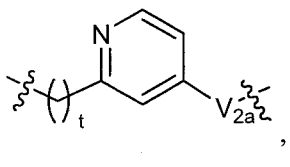
,

X-c



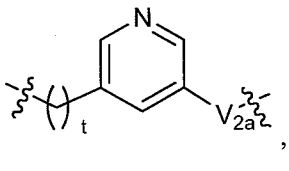
,

X-d



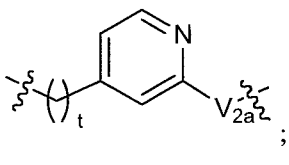
,

X-e



, or

X-f

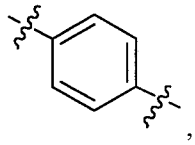


;

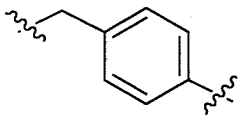
X-g

wherein V_{2a} and t have the values described herein.

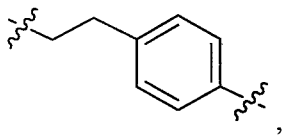
[00104] In certain embodiments, X is -C(O)-,



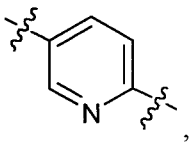
X-i



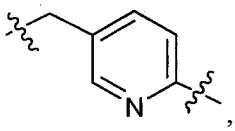
X-ii



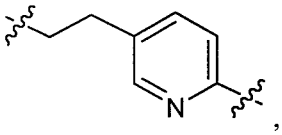
X-iii



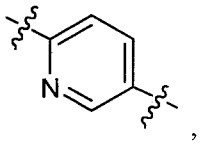
X-iv



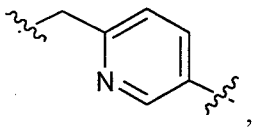
X-v



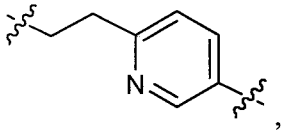
X-vi



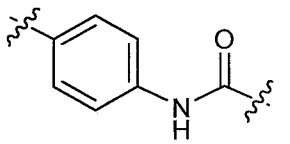
X-vii



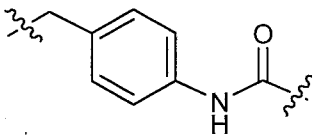
X-viii



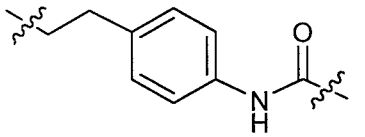
X-ix



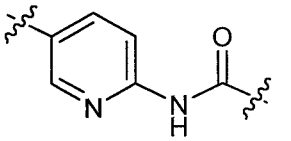
X-x



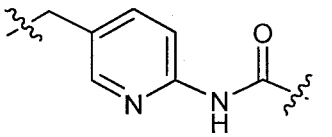
X-xi



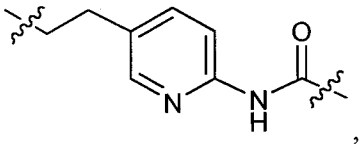
X-xii



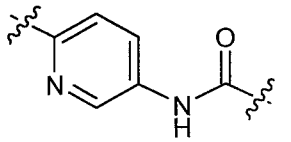
X-xiii



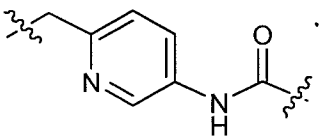
X-xiv



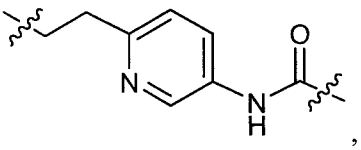
X-xv



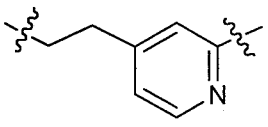
X-xvi



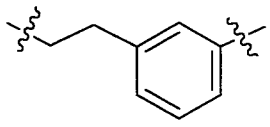
X-xvii



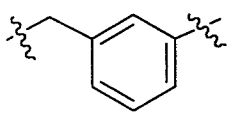
X-xviii



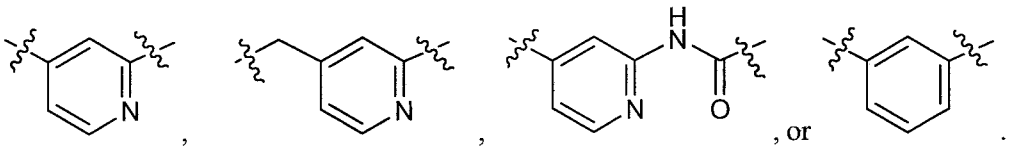
X-xix



X-xx



X-xxi

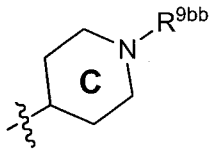


X-xxii X-xxiii X-xxiv X-xxv

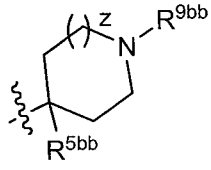
[00105] In certain embodiments, X is -C(O)-, **X-ii**, **X-iii**, **X-xi**, **X-xii**, **X-xxii**, **X-xxiv**, or **X-xxv**.

[00106] Ring C is a 4-7 membered heterocyclic ring containing one nitrogen atom, wherein the nitrogen atom is not the atom bound to X, and wherein the nitrogen atom in Ring C is substituted with R^{9bb} and Ring C is unsubstituted or substituted by 1-4 occurrences of R^{5b}; wherein R^{9bb}, X, and R^{5b} have the values described herein. In some embodiments, Ring C is a 4-7 membered heterocyclic ring containing one nitrogen atom, wherein the nitrogen atom is not the atom bound to X, and wherein the nitrogen atom in Ring C is substituted with R^{9bb} and Ring C is unsubstituted or substituted by 1-2 occurrences of R^{5b}; wherein R^{9bb}, X, and R^{5b} have the values described herein.

[00107] In certain embodiments, Ring C is:



wherein Ring C is unsubstituted or substituted with 1 occurrence of R^{5b}, wherein R^{9bb} and R^{5b} have the values described herein. In certain embodiments, Ring C is:



;

wherein R^{9bb}, z and R^{5bb} have the values described herein.

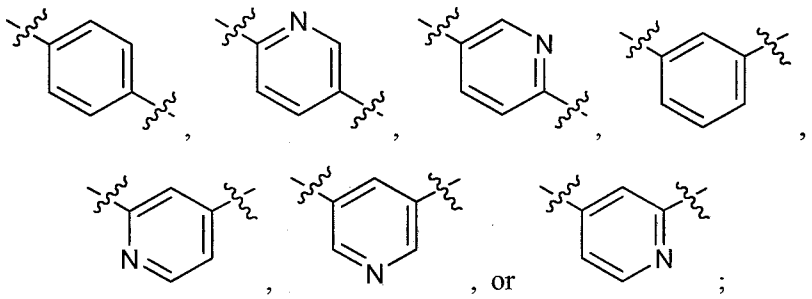
[00108] The variable V_{2a} is a bond, –NH-C(O)-, -NH-$S(O)_2$-, or –NH-C(O)-NH-. In some embodiments, V_{2a} is a bond or –NH-C(O)-. In certain embodiments, V_{2a} is a bond. In certain embodiments, V_{2a} is –NH-C(O)-.

[00109] The variable t is 0-2. In some embodiments, t is 0-1. In certain embodiments, t is 0. In certain embodiments, t is 1. In certain embodiments, t is 2.

[00110] The variable L_{2a} is a bond or unsubstituted or substituted C_{1-3} alkylene chain. In some embodiments, L_{2a} is a bond, -CH_2-, -CH_2CH_2-, or -$CH_2CH_2CH_2$-. In certain embodiments, L_{2a} is a bond. In certain embodiments, L_{2a} is –CH_2-. In certain embodiments, L_{2a} is -CH_2CH_2-.

[00111] The variable R^{3aa} is a 6-membered aromatic ring containing 0-2 nitrogen atoms which is unsubstituted or substituted with 1-2 independent occurrences of R^{4c}, wherein R^{4c} has the values

described herein. In some embodiments, R^{3aa} is phenyl or pyridyl, each of which is unsubstituted or substituted with 1-2 independent occurrences of R^{4c}, wherein R^{4c} has the values described herein. In some embodiments, R^{3aa} is:



wherein each ring is unsubstituted or substituted with 1-2 independent occurrences of R^{4c}.

[00112] The variable R^{4c} is chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethoxy, trifluoromethyl, methyl, or ethyl. In some embodiments, R^{4c} is chloro, fluoro, methyl or ethyl.

[00113] The variable z is 0-1. In some embodiments, z is 0. In some embodiments, z is 1.

[00114] Each occurrence of the variable R^{5b} is independently chloro, fluoro, hydroxy, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy, $-C(O)NH_2$, or $-CO_2H$. In some embodiments, each occurrence of the variable R^{5b} is independently chloro, fluoro, hydroxy, methyl, or ethyl. In certain embodiments, each occurrence of the variable R^{5b} is methyl.

[00115] The variable R^{5bb} is hydrogen or methyl. In some embodiments, R^{5bb} is hydrogen. In some embodiments, R^{5bb} is methyl.

[00116] The variable R^{9bb} is hydrogen, unsubstituted $C(O)$-O-C_{1-6} aliphatic, unsubstituted $C(O)$-C_{1-6} aliphatic, unsubstituted $C(O)$-C_{3-10} cycloaliphatic, or unsubstituted C_{1-6} aliphatic. In some embodiments, R^{9bb} is hydrogen, methyl, ethyl, isopropyl, or tert-butoxycarbonyl. In some embodiments, R^{9bb} is methyl, ethyl, or isopropyl. In certain embodiments, R^{9bb} is hydrogen.

[00117] In certain embodiments for the compounds of formulas (*I*), (*II*), (*III*) and (*IV*):

G is $-R^3$, $-V_1$-R^3, $-V_1$-L_1-R^3, or $-L_1$-R^3; and

V_1 is $-C(O)-$, $-C(O)$-$N(R^{4a})-$, or $-S(O)_2-$.

[00118] In certain embodiments for the compounds of formulas (*I*), (*II*), (*III*) and (*IV*):

G is $-R^3$, $-V_1$-R^3, $-V_1$-L_1-R^3, or $-L_1$-R^3;

L_1 is $-CH_2-$ or $-CH_2CH_2-$; and

V_1 is $-C(O)-$, $-C(O)$-$N(R^{4a})-$, or $-S(O)_2-$.

[00119] In certain embodiments, for the compound of formula (*I*):

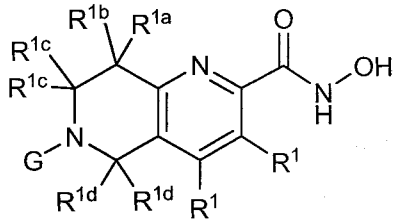
R^{1a} is hydrogen, fluoro, or methyl;

R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl; and

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl.

[00120] In certain embodiments, the compound of formula (*I*) is represented by:



;

(*II-a-i*)

wherein:

G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, or $-L_1-R^3$;

V_1 is -C(O)-, $-C(O)-N(R^{4a})-$, or $-S(O)_2-$;

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

R^{1a} is hydrogen, fluoro, or methyl;

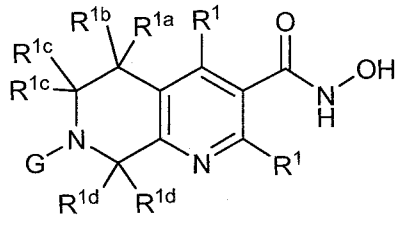
R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl; and

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl;

wherein R^3 and R^{4a} have the values contained herein.

[00121] In certain embodiments, the compound of formula (*I*) is represented by:



;

(*II-a-ii*)

wherein:

G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, or $-L_1-R^3$;

V_1 is -C(O)-, $-C(O)-N(R^{4a})-$, or $-S(O)_2-$;

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

R^{1a} is hydrogen, fluoro, or methyl;

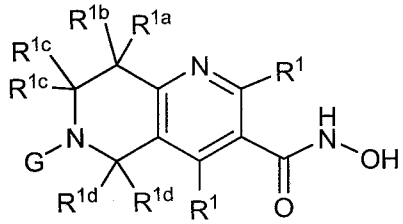
R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl; and

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl;

wherein R^3 and R^{4a} have the values contained herein.

[00122] In certain embodiments, the compound of formula (*I*) is represented by:



(*II-b-i*).

wherein:

G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, or $-L_1-R^3$;

V_1 is -C(O)-, $-C(O)-N(R^{4a})-$, or $-S(O)_2-$;

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

R^{1a} is hydrogen, fluoro, or methyl;

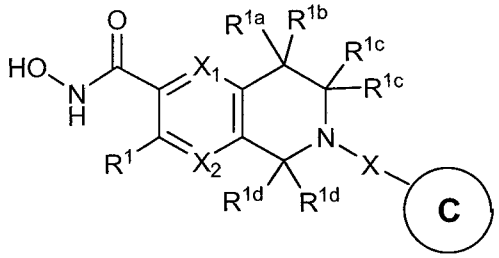
R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl; and

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl;

wherein R^3 and R^{4a} have the values contained herein.

[00123] In certain embodiments, the compound of formula (*I*) is represented by:



(*V-a*);

wherein:

one of X_1 and X_2 is CR^1 and the other is N; or both X_1 and X_2 are N;

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

R^{1a} is hydrogen, fluoro, or methyl;

R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl;

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl; and

X and Ring C have the values described herein.

[00124] In certain such embodiments:

R^{1a} is hydrogen;

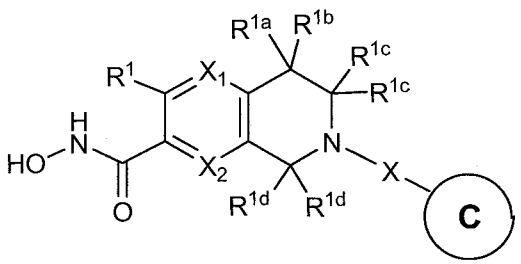
R^{1b} is hydrogen;

R^{1c} is hydrogen;

R^{1d} is hydrogen; and

R^1 is hydrogen.

[00125] In certain embodiments, the compound of formula (*I*) is represented by:



(*V-b*);

wherein:

one of X_1 and X_2 is CR^1 and the other is N; or both X_1 and X_2 are N;

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

R^{1a} is hydrogen, fluoro, or methyl;

R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl;

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl; and

X and Ring C have the values described herein.

[00126] In certain such embodiments:

R^{1a} is hydrogen;

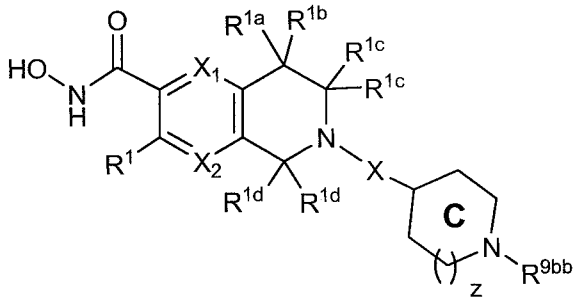
R^{1b} is hydrogen;

R^{1c} is hydrogen;

R^{1d} is hydrogen; and

R^1 is hydrogen.

[00127] In certain embodiments, the compound of formula (*I*) is represented by:



(*VI-a);*

wherein:

one of X_1 and X_2 is CR^1 and the other is N; or both X_1 and X_2 are N;

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

R^{1a} is hydrogen, fluoro, or methyl;

R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl;

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl;

R^{9bb} is hydrogen, methyl, ethyl, isopropyl, or tert-butoxycarbonyl;

X is -C(O)-, **X-a**, **X-b**, **X-c**, **X-d**, **X-e**, **X-f,** or **X-g**;

Ring C is unsubstituted or substituted with one occurrence of R^{5b}; and

z, R^{5b}, t, and V_2 have the values described herein.

[00128] In certain such embodiments,

R^{5b} is methyl;

R^{1a} is hydrogen;

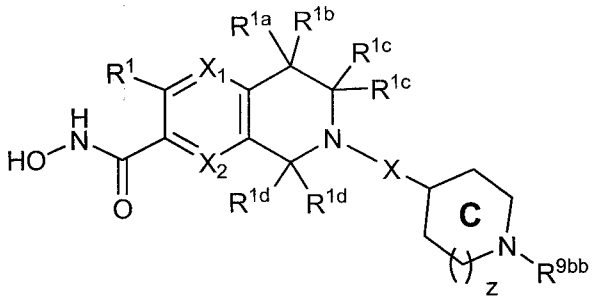
R^{1b} is hydrogen;

R^{1c} is hydrogen;

R^{1d} is hydrogen; and

R^{1} is hydrogen.

[00129] In certain embodiments, the compound of formula (*I*) is represented by:



(*VI-b*);

wherein:

one of X_1 and X_2 is CR^1 and the other is N; or both X_1 and X_2 are N;

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

R^{1a} is hydrogen, fluoro, or methyl;

R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl;

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl;

R^{9bb} is hydrogen, methyl, ethyl, isopropyl, or tert-butoxycarbonyl;

X is -C(O)-, **X-a**, **X-b**, **X-c**, **X-d**, **X-e**, **X-f**, or **X-g**;

Ring C is unsubstituted or substituted with one occurrence of R^{5b}; and

z, R^{5b}, t, and V_2 have the values described herein.

[00130] In certain such embodiments,

R^{5b} is methyl;

R^{1a} is hydrogen;

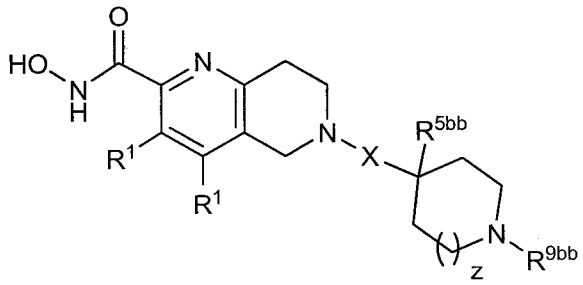
R^{1b} is hydrogen;

R^{1c} is hydrogen;

R^{1d} is hydrogen; and

R^{1} is hydrogen.

[00131] In certain embodiments, the compound of formula (*I*) is represented by:



(*VII-a*);

each occurrence of R^{1} is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

R^{9bb} is hydrogen, methyl, ethyl, isopropyl, or tert-butoxycarbonyl;

X is -C(O)-, **X-ii**, **X-iii**, **X-xi**, **X-xii**, **X-xxii**, **X-xxiv**, or **X-xxv**;

R^{5bb} is hydrogen or methyl; and

z has the values described herein.

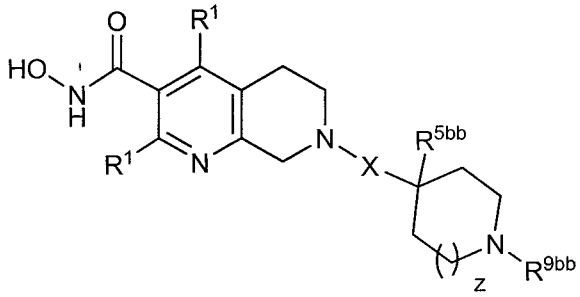
[00132] In certain such embodiments:

R^1 is hydrogen

R^{5bb} is methyl; and

z is 1.

[00133] In certain embodiments, the compound of formula (*I*) is represented by:



(*VII-b*);

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

R^{9bb} is hydrogen, methyl, ethyl, isopropyl, or tert-butoxycarbonyl;

X is -C(O)-, **X-ii**, **X-iii**, **X-xi**, **X-xii**, **X-xxii**, **X-xxiv**, or **X-xxv**;

R^{5bb} is hydrogen or methyl; and

z has the values described herein.

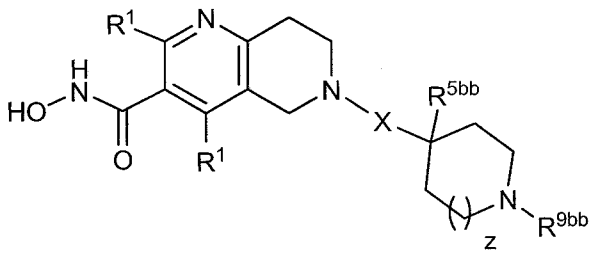
[00134] In certain such embodiments:

R^1 is hydrogen;

R^{5bb} is methyl; and

z is 1.

[00135] In certain embodiments, the compound of formula (*I*) is represented by:



(*VII-c*);

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

R^{9bb} is hydrogen, methyl, ethyl, isopropyl, or tert-butoxycarbonyl;

X is -C(O)-, **X-ii**, **X-iii**, **X-xi**, **X-xii**, **X-xxii**, **X-xxiv**, or **X-xxv**;

R^{5bb} is hydrogen or methyl; and

z has the values described herein.

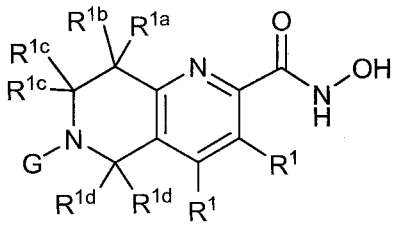
[00136] In certain such embodiments:

R^1 is hydrogen;

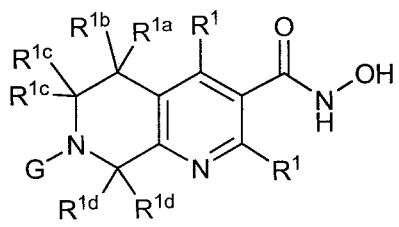
R^{5bb} is methyl; and

z is 1.

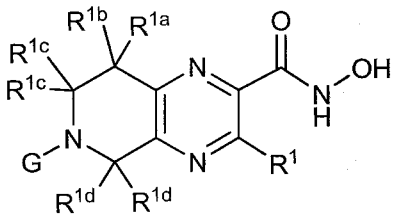
[00137] In some embodiments, the compound of formula (*I*) is represented by formula (*II-a-i*)-(*II-b-iii*):



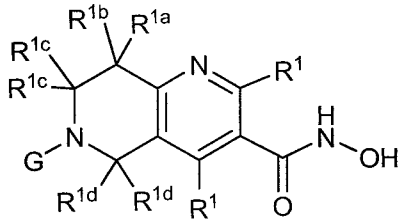
(*II-a-i*),



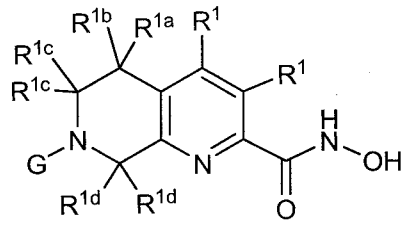
(*II-a-ii*),



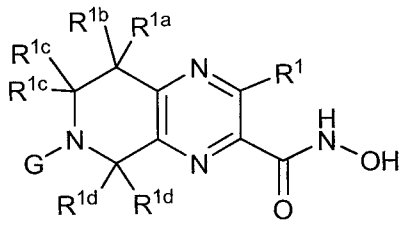
(*II-a-iii*),



(*II-b-i*),



(*II-b-ii*), or



(*II-b-iii*);

wherein:

G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, or $-L_1-R^3$;

V_1 is -C(O)-, $-C(O)-N(R^{4a})-$, or $-S(O)_2-$;

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

R^{1a} is hydrogen, fluoro, or methyl;

R^{1b} is hydrogen, fluoro, or methyl;

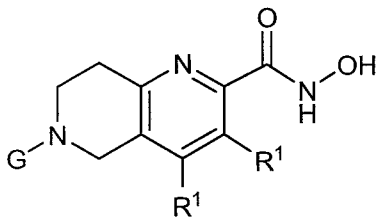
each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl; and

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl;

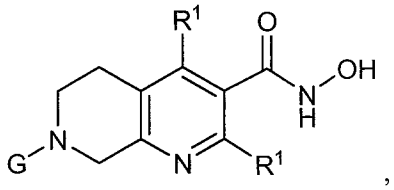
wherein R^3, L_1, and R^{4a} have the values contained herein.

[00138] In certain such embodiments, the compound of formula (*I*) is represented by formula (***II-a-i***). In certain such embodiments, the compound of formula (*I*) is represented by formula (***II-a-ii***). In certain such embodiments, the compound of formula (*I*) is represented by formula (***II-a-iii***). In certain such embodiments, the compound of formula (*I*) is represented by formula (***II-b-i***). In certain such embodiments, the compound of formula (*I*) is represented by formula (***II-b-ii***). In certain such embodiments, the compound of formula (*I*) is represented by formula (***II-b-iii***).

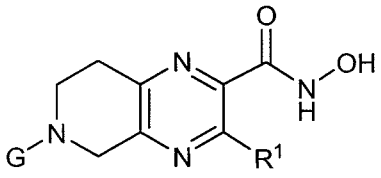
[00139] In some embodiments, the compound of formula (*I*) is represented by formula (***III-a-i***)-(***III-b-iii***):



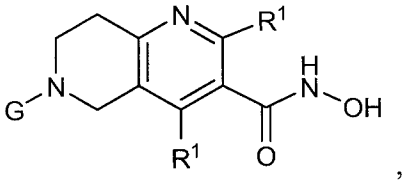
(***III-a-i***),



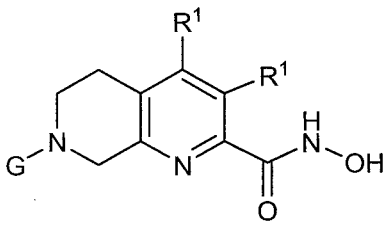
(***III-a-ii***),



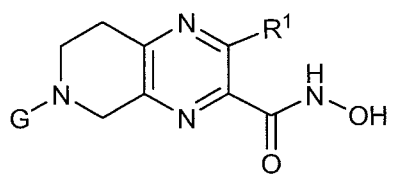
(***III-a-iii***),



(***III-b-i***),



(***III-b-ii***), or



(***III-b-iii***);

wherein:

G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, or $-L_1-R^3$;

V_1 is -C(O)-, -C(O)-NH-, or $-S(O)_2$;

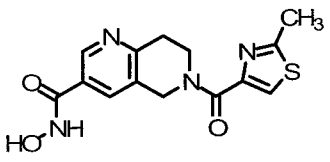
each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl;

wherein R^3 and L_1 have the values described herein.

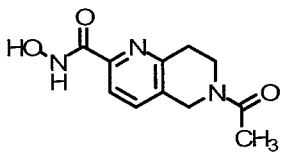
[00140] In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-a-i***). In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-a-ii***). In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-a-iii***). In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-b-i***). In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-b-ii***). In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-b-iii***).

[00141] In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-a-i***) wherein R^1 is hydrogen; and L_1 is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$. In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-a-ii***) wherein R^1 is hydrogen; and L_1 is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$. In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-a-iii***) wherein R^1 is hydrogen; and L_1 is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$. In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-b-i***) wherein R^1 is hydrogen; and L_1 is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$. In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-b-ii***) wherein R^1 is hydrogen; and L_1 is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$. In certain such embodiments, the compound of formula (*I*) is represented by formula (***III-b-iii***) wherein R^1 is hydrogen; and L_1 is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$.

[00142] Representative examples of compounds of formula (*I*) are shown in Table 1:



I-1



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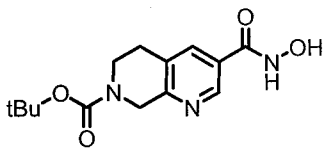

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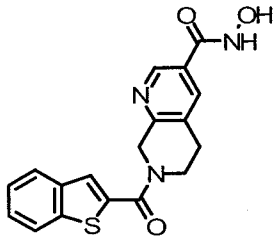

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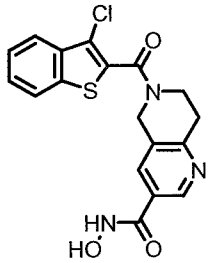

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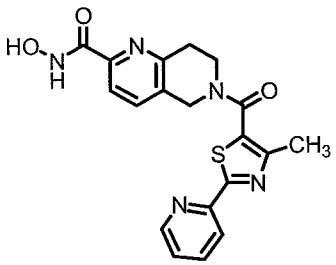

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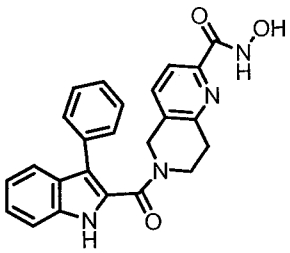

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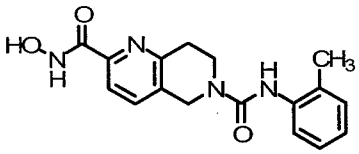

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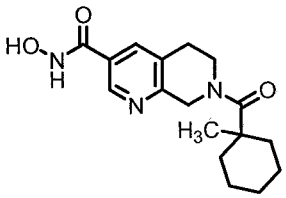

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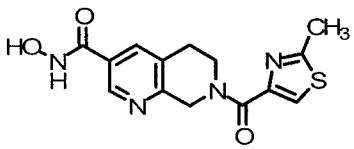

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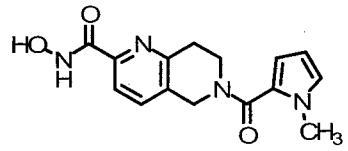

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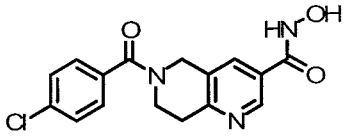

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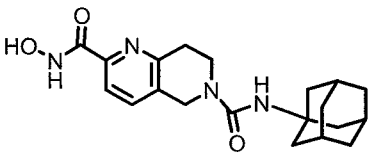

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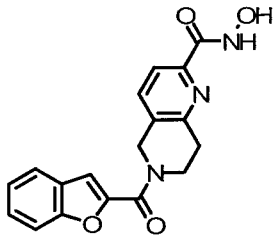

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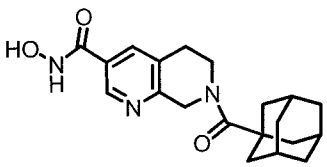

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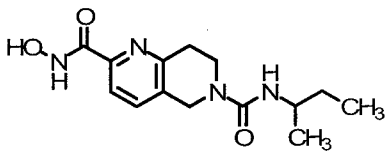

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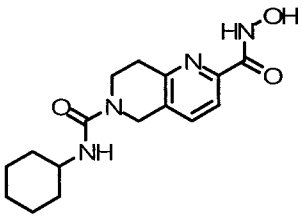

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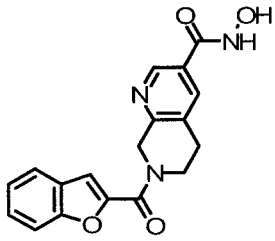

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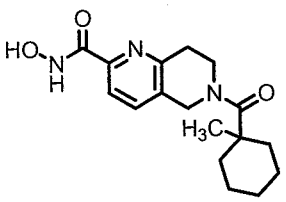

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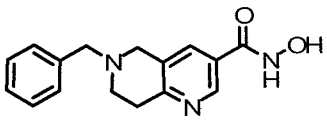

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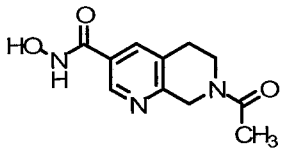

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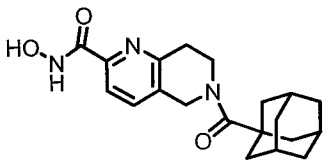

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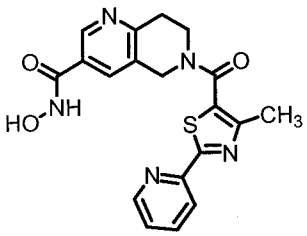

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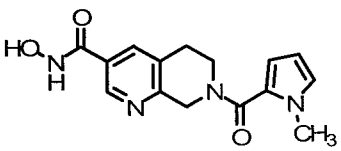

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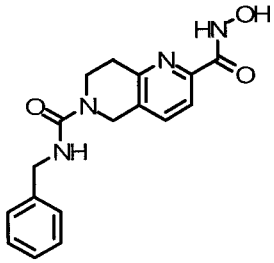

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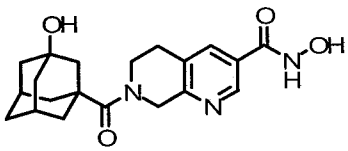

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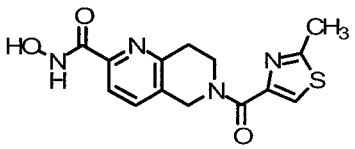

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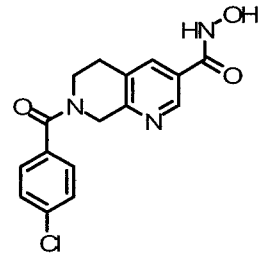

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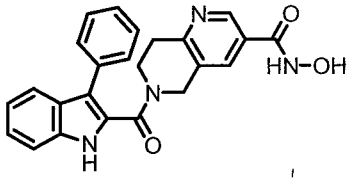

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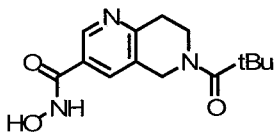

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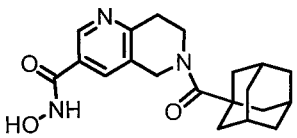

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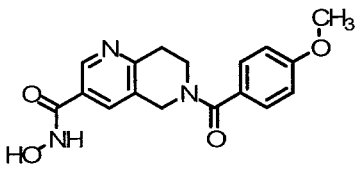

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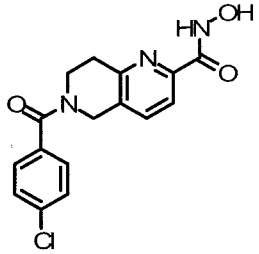

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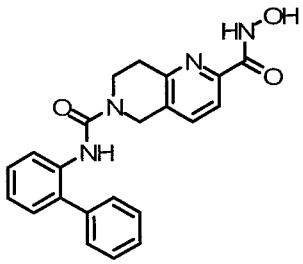

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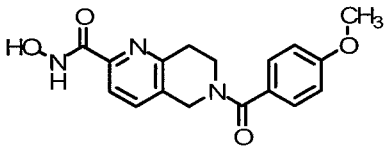

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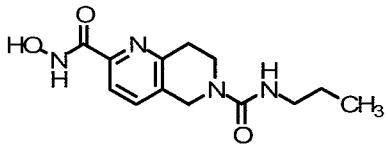

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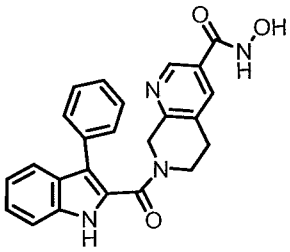

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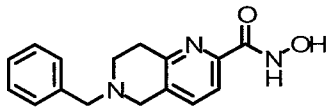

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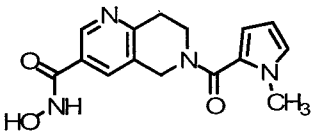

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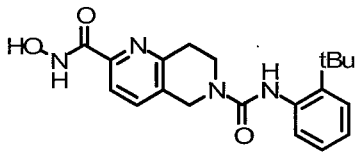

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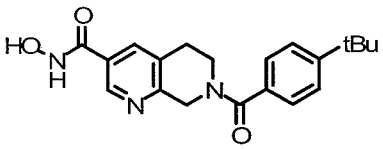

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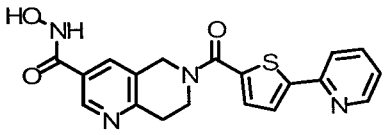

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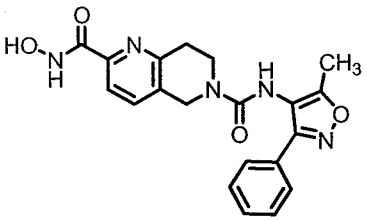

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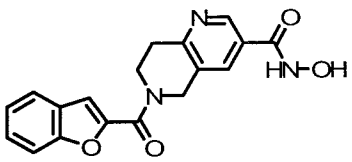

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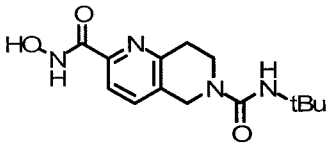

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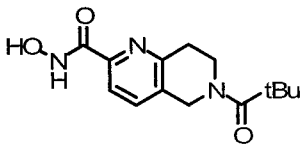

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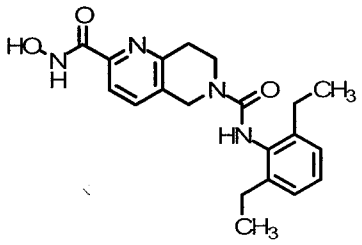

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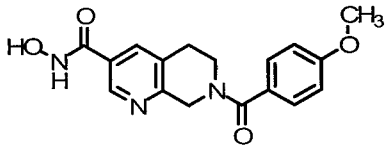

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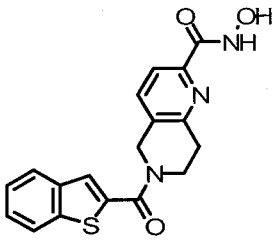

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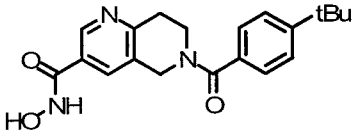

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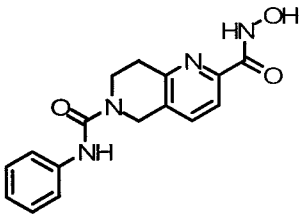

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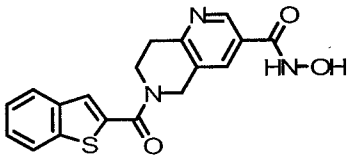

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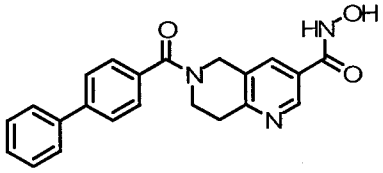

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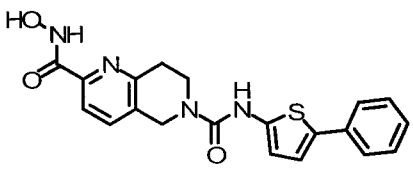

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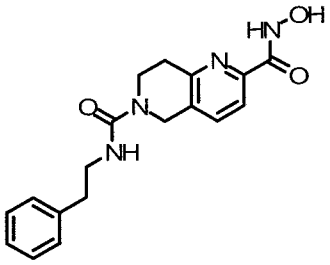
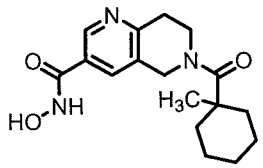


I-55



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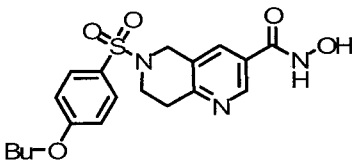

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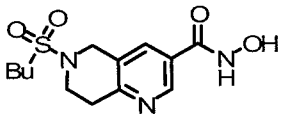

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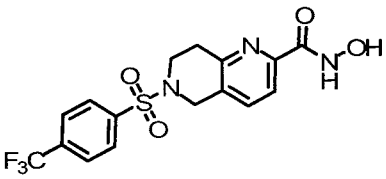

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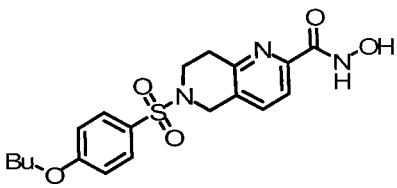

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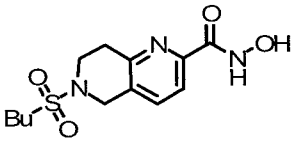

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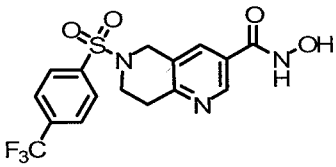

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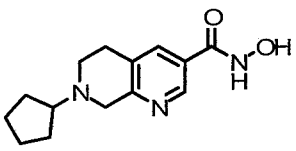

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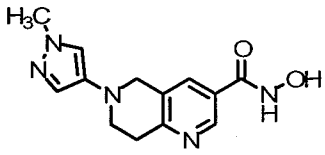

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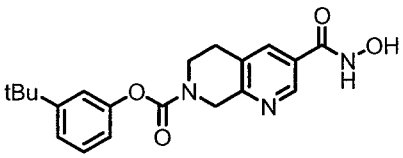

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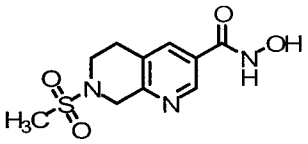

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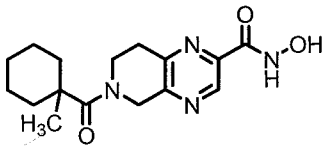

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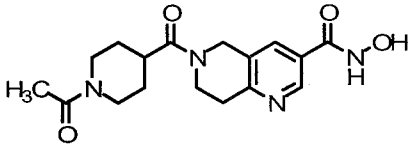

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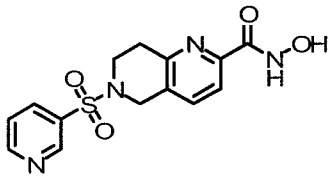

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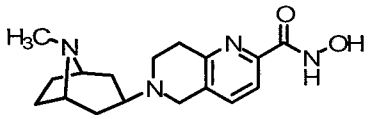

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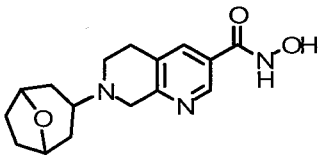

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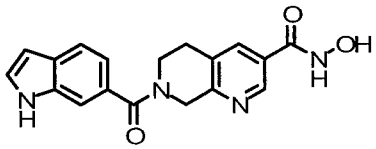

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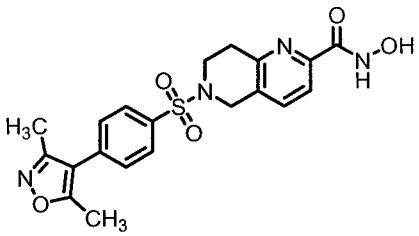

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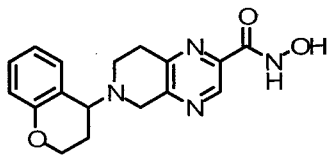

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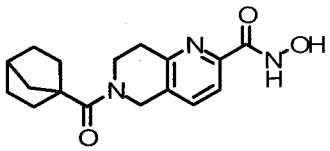

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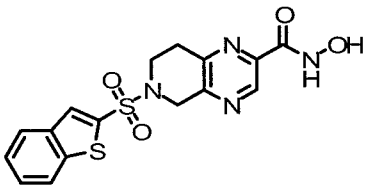

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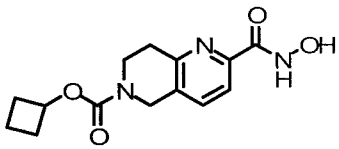

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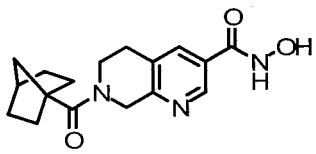

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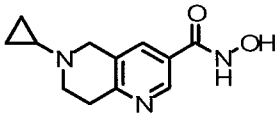

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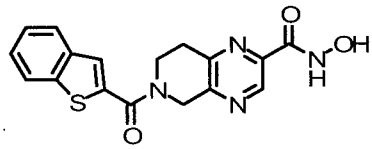

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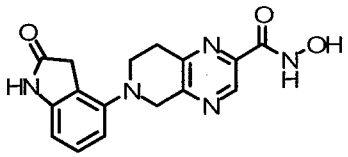

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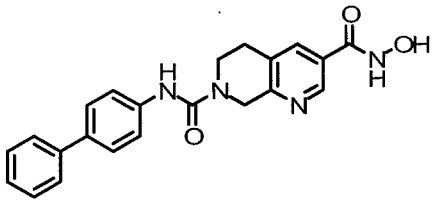

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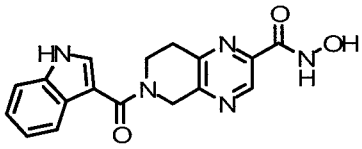

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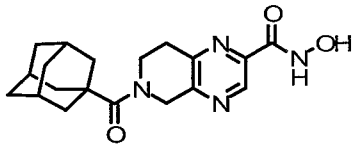

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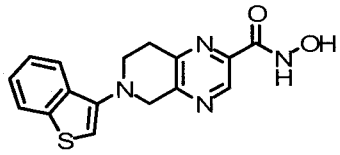

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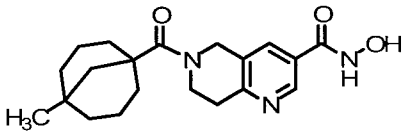

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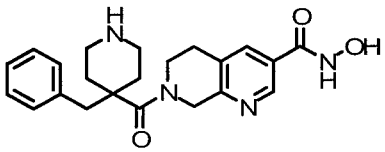

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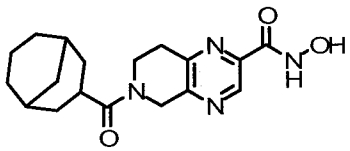

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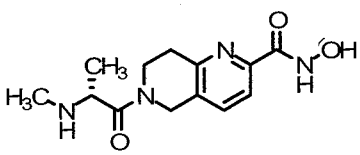

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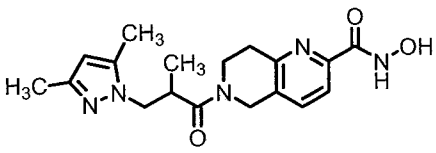

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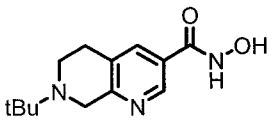

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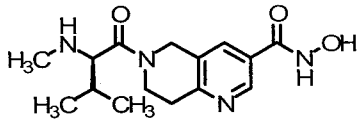

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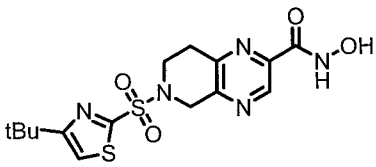

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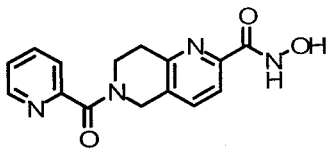

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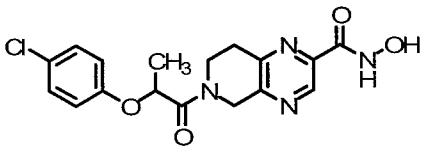

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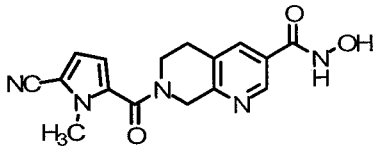

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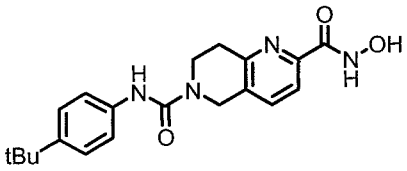

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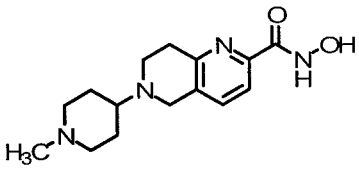

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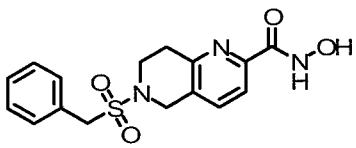

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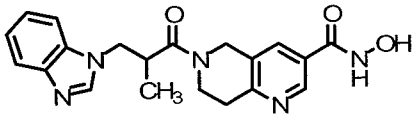

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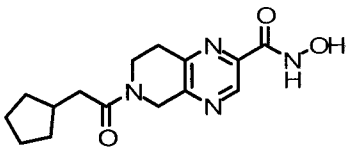

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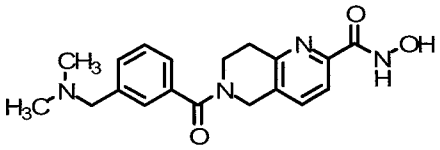

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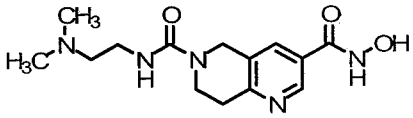

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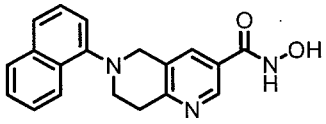

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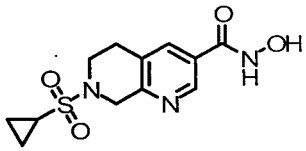

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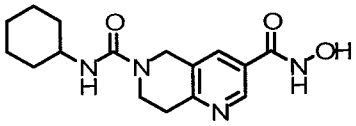

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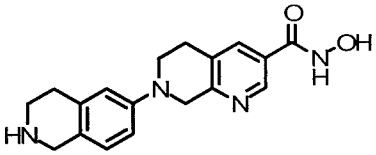

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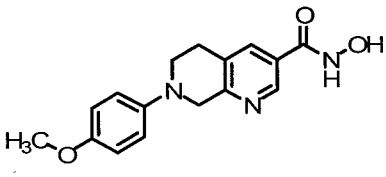

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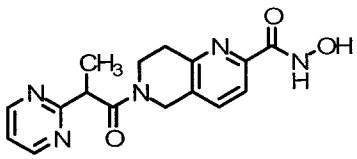

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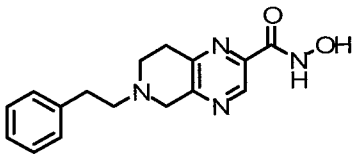

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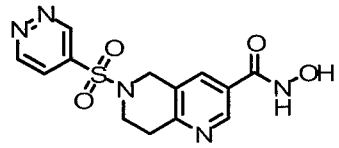

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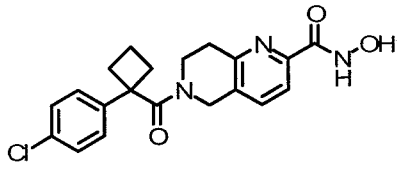

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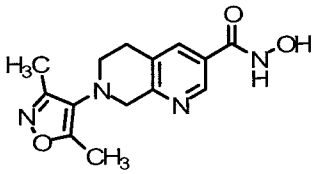
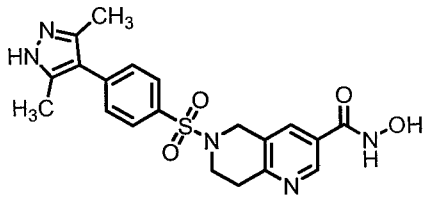
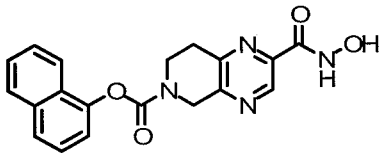


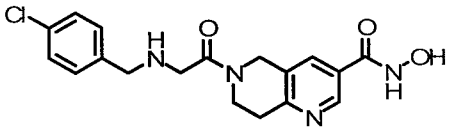
I-113



I-114



I-115



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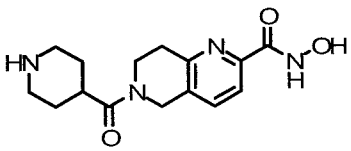

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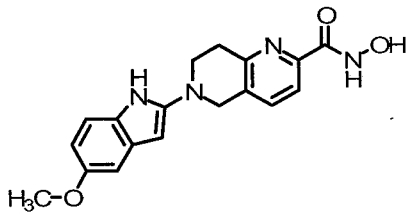
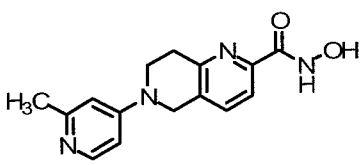
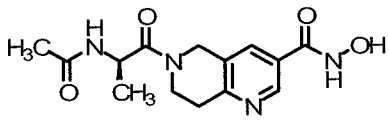


I-118



I-119



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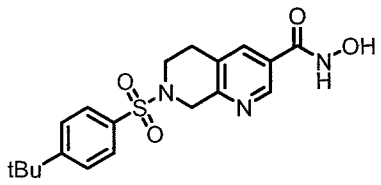

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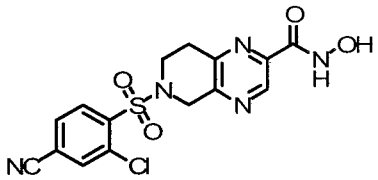

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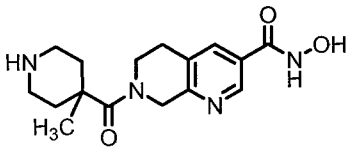
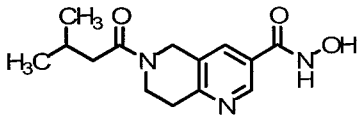
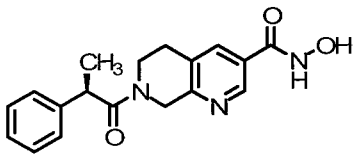


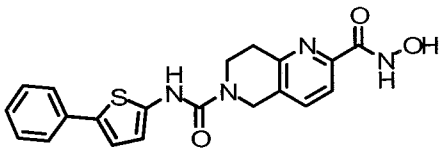
I-123



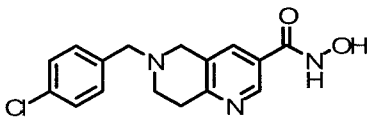
I-124



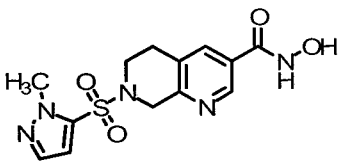
I-125



I-126



I-127



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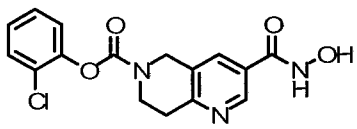

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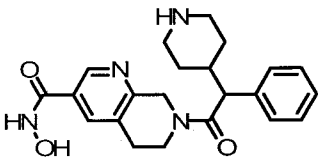

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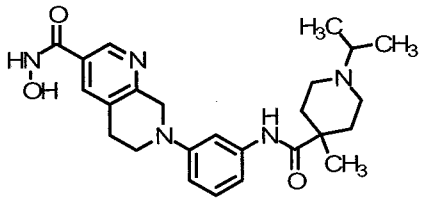

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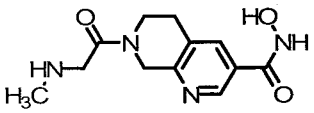

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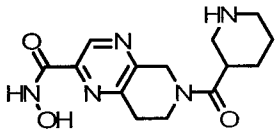

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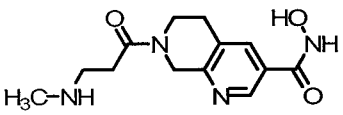

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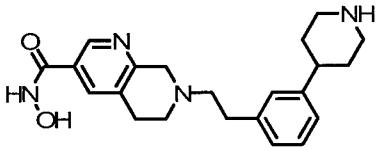

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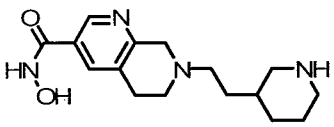

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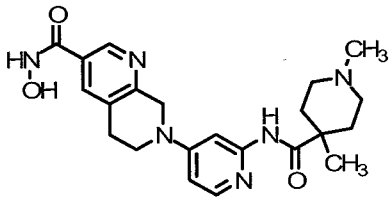
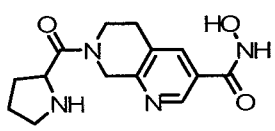


I-137



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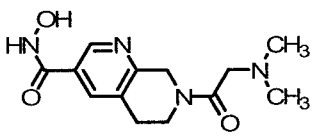

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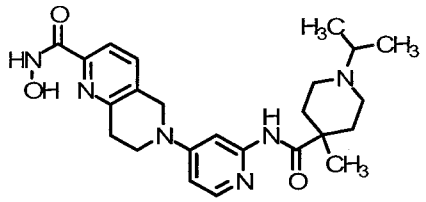

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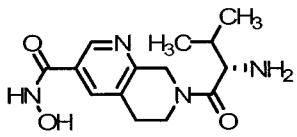

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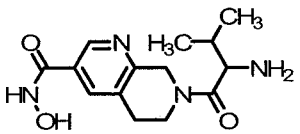

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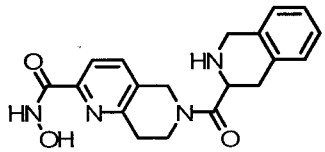

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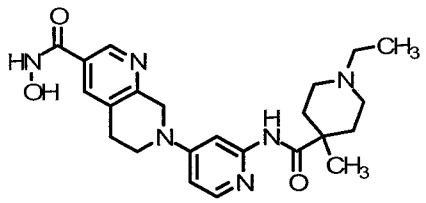
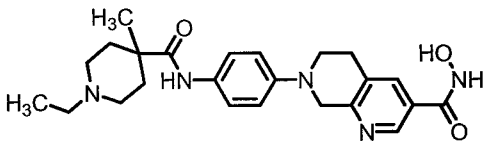


I-144



I-145

[00143] The compounds in Table 1 above may also be identified by the following chemical names:

I-1	*N*-hydroxy-6-[(2-methyl-1,3-thiazol-4-yl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-2	6-acetyl-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-3	*tert*-butyl 3-[(hydroxyamino)carbonyl]-5,8-dihydro-1,7-naphthyridine-7(6*H*)-carboxylate
I-4	7-(1-benzothien-2-ylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-5	6-[(3-chloro-1-benzothien-2-yl)carbonyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-6	*N*-hydroxy-6-[(4-methyl-2-pyridin-2-yl-1,3-thiazol-5-yl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-7	*N*-hydroxy-6-[(3-phenyl-1*H*-indol-2-yl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide

I-8	N^2-hydroxy-N^6-(2-methylphenyl)-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-9	*N*-hydroxy-7-[(1-methylcyclohexyl)carbonyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-10	*N*-hydroxy-7-[(2-methyl-1,3-thiazol-4-yl)carbonyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-11	*N*-hydroxy-6-[(1-methyl-1*H*-pyrrol-2-yl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-12	6-(4-chlorobenzoyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-13	N^6-[1-adamantyl]-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-14	6-(1-benzofuran-2-ylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-15	7-[1-adamantylcarbonyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-16	N^6-(*sec*-butyl)-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-17	N^6-cyclohexyl-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-18	7-(1-benzofuran-2-ylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-19	*N*-hydroxy-6-[(1-methylcyclohexyl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-20	6-benzyl-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-21	7-acetyl-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-22	6-[1-adamantylcarbonyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-23	*N*-hydroxy-6-[(4-methyl-2-pyridin-2-yl-1,3-thiazol-5-yl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-24	*N*-hydroxy-7-[(1-methyl-1*H*-pyrrol-2-yl)carbonyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-25	N^6-benzyl-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-26	*N*-hydroxy-7-[(3-hydroxy-1-adamantyl)carbonyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-27	*N*-hydroxy-6-[(2-methyl-1,3-thiazol-4-yl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-28	7-(4-chlorobenzoyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-29	*N*-hydroxy-6-[(3-phenyl-1*H*-indol-2-yl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-30	6-(2,2-dimethylpropanoyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-31	6-[1-adamantylcarbonyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-32	*N*-hydroxy-6-(4-methoxybenzoyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-33	6-(4-chlorobenzoyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-34	N^6-biphenyl-2-yl-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-35	*N*-hydroxy-6-(4-methoxybenzoyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-36	N^2-hydroxy-N^6-propyl-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-37	*N*-hydroxy-7-[(3-phenyl-1*H*-indol-2-yl)carbonyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-38	6-benzyl-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide

I-39	*N*-hydroxy-6-[(1-methyl-1*H*-pyrrol-2-yl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-40	N^6-(2-*tert*-butylphenyl)-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-41	7-(4-*tert*-butylbenzoyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-42	*N*-hydroxy-6-[(5-pyridin-2-yl-2-thienyl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-43	N^2-hydroxy-N^6-(5-methyl-3-phenylisoxazol-4-yl)-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-44	6-(1-benzofuran-2-ylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-45	N^6-(*tert*-butyl)-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-46	6-(2,2-dimethylpropanoyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-47	N^6-(2,6-diethylphenyl)-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-48	*N*-hydroxy-7-(4-methoxybenzoyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-49	6-(1-benzothien-2-ylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-50	6-(4-*tert*-butylbenzoyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-51	N^2-hydroxy-N^6-phenyl-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-52	6-(1-benzothien-2-ylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-53	6-(biphenyl-4-ylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-54	N^2-hydroxy-N^6-(5-phenyl-2-thienyl)-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-55	N^2-hydroxy-N^6-(2-phenylethyl)-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-56	*N*-hydroxy-6-[(1-methylcyclohexyl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-57	6-[(4-butoxyphenyl)sulfonyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-58	6-(butylsulfonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-59	*N*-hydroxy-6-{[4-(trifluoromethyl)phenyl]sulfonyl}-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-60	6-[(4-butoxyphenyl)sulfonyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-61	6-(butylsulfonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-62	*N*-hydroxy-6-{[4-(trifluoromethyl)phenyl]sulfonyl}-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-63	7-cyclopentyl-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-64	*N*-hydroxy-6-(1-methyl-1*H*-pyrazol-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-65	3-*tert*-butylphenyl 3-[(hydroxyamino)carbonyl]-5,8-dihydro-1,7-naphthyridine-7(6*H*)-carboxylate
I-66	*N*-hydroxy-7-(methylsulfonyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-67	*N*-hydroxy-6-[(1-methylcyclohexyl)carbonyl]-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-68	6-[(1-acetylpiperidin-4-yl)carbonyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-69	*N*-hydroxy-6-(pyridin-3-ylsulfonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-70	*N*-hydroxy-6-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-

	carboxamide
I-71	*N*-hydroxy-7-(8-oxabicyclo[3.2.1]oct-3-yl)-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-72	*N*-hydroxy-7-(1*H*-indol-6-ylcarbonyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-73	6-{[4-(3,5-dimethylisoxazol-4-yl)phenyl]sulfonyl}-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-74	6-(3,4-dihydro-2*H*-chromen-4-yl)-*N*-hydroxy-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-75	6-(bicyclo[2.2.1]hept-1-ylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-76	6-(1-benzothien-2-ylsulfonyl)-*N*-hydroxy-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-77	cyclobutyl 2-[(hydroxyamino)carbonyl]-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate
I-78	7-(bicyclo[2.2.1]hept-1-ylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-79	6-cyclopropyl-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-80	6-(1-benzothien-2-ylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-81	*N*-hydroxy-6-(2-oxo-2,3-dihydro-1*H*-indol-4-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-82	N^7-biphenyl-4-yl-N^3-hydroxy-5,8-dihydro-1,7-naphthyridine-3,7(6*H*)-dicarboxamide
I-83	*N*-hydroxy-6-(1*H*-indol-3-ylcarbonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-84	6-(1-adamantylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-85	6-(1-benzothien-3-yl)-*N*-hydroxy-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-86	*N*-hydroxy-6-[(5-methylbicyclo[3.3.1]non-1-yl)carbonyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-87	7-[(4-benzylpiperidin-4-yl)carbonyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-88	6-(bicyclo[3.3.1]non-3-ylcarbonyl)-*N*-hydroxy-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-89	*N*-hydroxy-6-[(2*R*)-2-(methylamino)propanoyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-90	6-[3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-methylpropanoyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-91	7-*tert*-butyl-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-92	*N*-hydroxy-6-[(2*R*)-3-methyl-2-(methylamino)butanoyl]-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-93	6-[(4-*tert*-butyl-1,3-thiazol-2-yl)sulfonyl]-*N*-hydroxy-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-94	*N*-hydroxy-6-(pyridin-2-ylcarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-95	6-[2-(4-chlorophenoxy)propanoyl]-*N*-hydroxy-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-96	7-[(5-cyano-1-methyl-1*H*-pyrrol-2-yl)carbonyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-

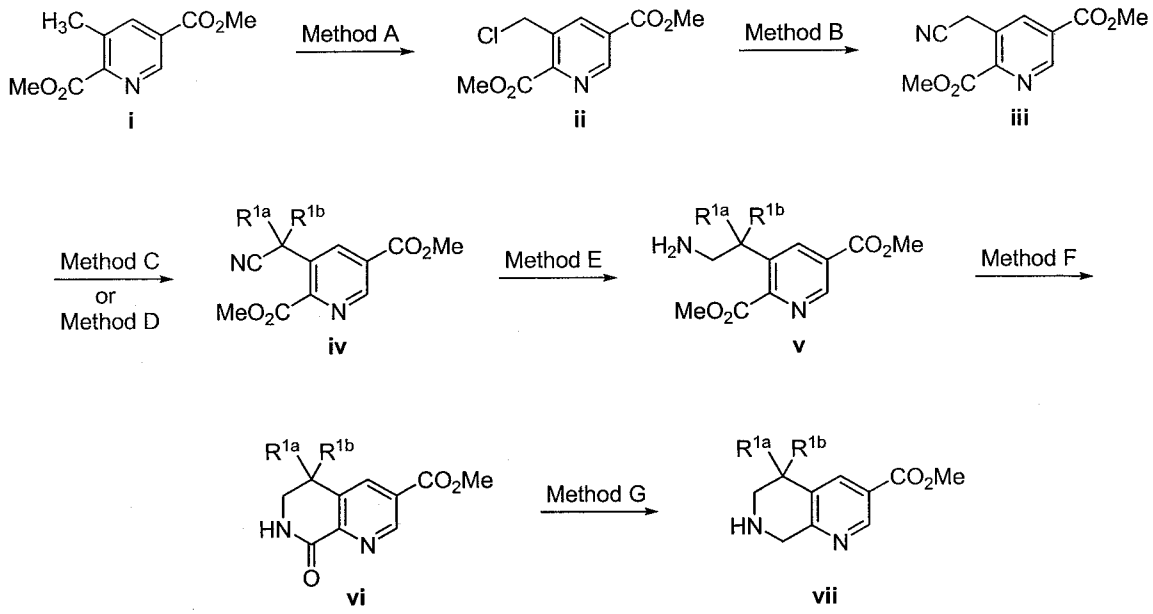
	naphthyridine-3-carboxamide
I-97	N^6-(4-*tert*-butylphenyl)-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-98	*N*-hydroxy-6-(1-methylpiperidin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-99	6-(benzylsulfonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-100	6-[3-(1*H*-benzimidazol-1-yl)-2-methylpropanoyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-101	6-(cyclopentylacetyl)-*N*-hydroxy-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-102	6-{3-[(dimethylamino)methyl]benzoyl}-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-103	N^6-[2-(dimethylamino)ethyl]-N^3-hydroxy-7,8-dihydro-1,6-naphthyridine-3,6(5*H*)-dicarboxamide
I-104	*N*-hydroxy-6-(1-naphthyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-105	7-(cyclopropylsulfonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-106	N^6-cyclohexyl-N^3-hydroxy-7,8-dihydro-1,6-naphthyridine-3,6(5*H*)-dicarboxamide
I-107	*N*-hydroxy-7-(1,2,3,4-tetrahydroisoquinolin-6-yl)-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-108	*N*-hydroxy-7-(4-methoxyphenyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-109	*N*-hydroxy-6-(2-pyrimidin-2-ylpropanoyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-110	*N*-hydroxy-6-(2-phenylethyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-111	*N*-hydroxy-6-(pyridazin-4-ylsulfonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-112	6-{[1-(4-chlorophenyl)cyclobutyl]carbonyl}-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-113	7-(3,5-dimethylisoxazol-4-yl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-114	6-{[4-(3,5-dimethyl-1*H*-pyrazol-4-yl)phenyl]sulfonyl}-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-115	1-naphthyl 2-[(hydroxyamino)carbonyl]-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxylate
I-116	6-{[(4-chlorobenzyl)amino]acetyl}-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-117	*N*-hydroxy-6-(piperidin-4-ylcarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-118	*N*-hydroxy-6-(5-methoxy-1*H*-indol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-119	*N*-hydroxy-6-(2-methylpyridin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-120	6-[(2*R*)-2-(acetylamino)propanoyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-121	7-[(4-*tert*-butylphenyl)sulfonyl]-*N*-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-122	6-[(2-chloro-4-cyanophenyl)sulfonyl]-*N*-hydroxy-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-2-carboxamide
I-123	*N*-hydroxy-7-[(4-methylpiperidin-4-yl)carbonyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-124	*N*-hydroxy-6-(3-methylbutanoyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide
I-125	*N*-hydroxy-7-[(2*R*)-2-phenylpropanoyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-126	N^2-hydroxy-N^6-(5-phenyl-2-thienyl)-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide
I-127	6-(4-chlorobenzyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide

I-128	*N*-hydroxy-7-[(1-methyl-1*H*-pyrazol-5-yl)sulfonyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-129	2-chlorophenyl 3-[(hydroxyamino)carbonyl]-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate
I-130	N-hydroxy-7-[phenyl(piperidin-4-yl)acetyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-131	N-hydroxy-7-(3-{[(1-isopropyl-4-methylpiperidin-4-yl)carbonyl]amino}phenyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-132	N-hydroxy-7-[(methylamino)acetyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-133	N-hydroxy-6-(piperidin-3-ylcarbonyl)-5,6,7,8-tetrahydropyrido[3,4-b]pyrazine-2-carboxamide
I-134	N-hydroxy-7-[3-(methylamino)propanoyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-135	N-hydroxy-7-[2-(3-piperidin-4-ylphenyl)ethyl]-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-136	N-hydroxy-7-(2-piperidin-3-ylethyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-137	7-(2-{[(1,4-dimethylpiperidin-4-yl)carbonyl]amino}pyridin-4-yl)-N-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-138	N-hydroxy-7-(pyrrolidin-2-ylcarbonyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-139	7-[(dimethylamino)acetyl]-N-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-140	N-hydroxy-6-(2-{[(1-isopropyl-4-methylpiperidin-4-yl)carbonyl]amino}pyridin-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-141	7-[(2S)-2-amino-3-methylbutanoyl]-N-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-142	7-(2-amino-3-methylbutanoyl)-N-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-143	N-hydroxy-6-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide
I-144	7-(2-{[(1-ethyl-4-methylpiperidin-4-yl)carbonyl]amino}pyridin-4-yl)-N-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
I-145	7-(4-{[(1-ethyl-4-methylpiperidin-4-yl)carbonyl]amino}phenyl)-N-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide

4. General Synthetic Methods and Intermediates

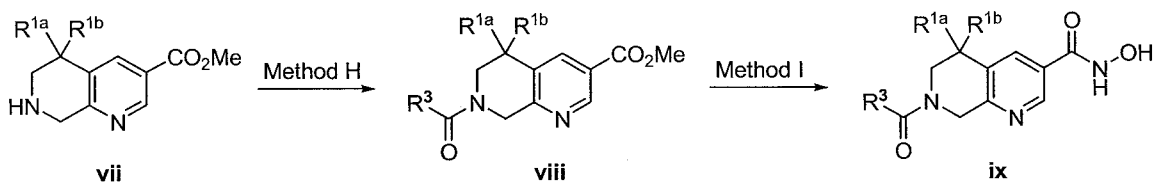
[00144] The compounds of the present invention can be prepared by methods known to one of ordinary skill in the art and / or by reference to the schemes shown below and the synthetic examples. Exemplary synthetic routes are set forth in Schemes below and in the Examples.

Scheme 1: General method for the preparation of 5-substituted methyl-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxylates



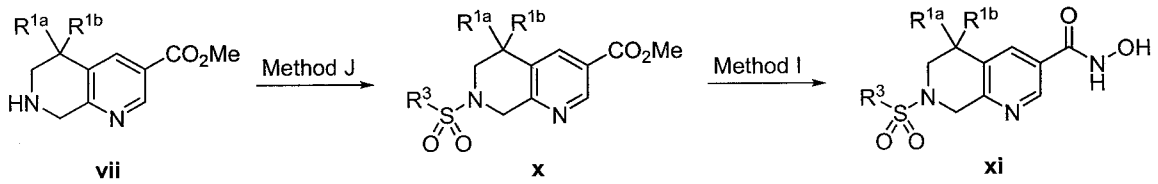
[00145] Scheme 1 shows a general route for the preparation of compounds of formula **vii** starting from dimethyl 3-methylpyridine-2,5-dicarboxylate **i** obtained as described by Wu *et al., Org. Lett.* **1999** 1(5):745. Treatment of **i** with sulfuryl chloride in the presence of a radical initiator such as AIBN provides access to the chloromethyl containing material **ii** (Method A; Menges *et al.,* Intl. App. Pub. No. WO 10/054952). The benzylic chloride can be displaced with sodium cyanide (Method B) to generate arylacetonitrile **iii** which upon treatment with bases such as sodium hydride or potassium *t*-butoxide and subsequent reaction with alkyl halides affords either mono (Method C, Tobisu *et al., J. Am. Chem. Soc.* **2009**, 131(9):3174) or dialkylated (Method D, Nagata *et al., Tetrahedron: Asymmetry*, 2009, 20(21): 2530) compounds of formula **iv**. Reduction of the nitrile using Raney Nickel (Method E, Price *et al., Bioorg. Med. Chem. Lett.* **2007**, 17(2):363) followed by cyclization with heating in the presence of a base such as sodium *t*-butoxide (Method F, Fevig *et al.,* Intl. App. Pub. No. WO 08/064107) generates compounds of formula **vi**. Removal of the amide carbonyl in **vi** is accomplished via reduction in the presence of suitable hydride delivery agent such as $BH_3 \cdot THF$ (Method G) as described by Di Fabio *et al., J. Med. Chem.* **2009**, 52:3238 leading to the formation of compound **vii**.

Scheme 2: General method for the preparation of acyl derivatives of 5-substituted-5,6,7,8-tetrahydro-1,7-naphthyridine-3-hydroxamates



[00146] Scheme 2 shows a route for the preparation of compounds of formula **ix**. Reaction of the secondary amines represented by compounds of formula **vii** with carboxylic acids (R^3-CO_2H) employing coupling agents such as HBTU or HATU leads to the formation of the corresponding amide **viii** (Method H). Conversion of the methyl ester in **viii** to a hydroxamate is conducted by reaction with the potassium salt of hydroxylamine (Method I; Huang *et al.*, *J. Med. Chem.* **2009**, 52(21):6757) leading to the formation of compounds of formula **ix**.

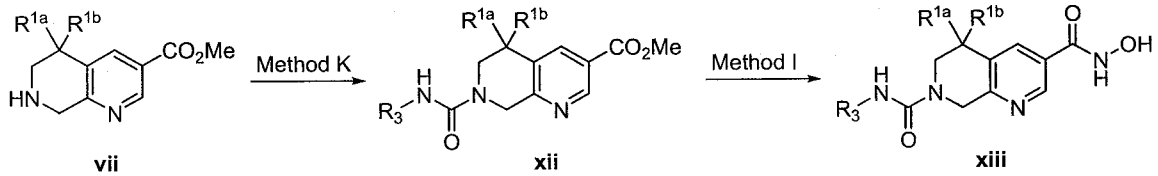
Scheme 3: General method for the preparation of sulfonamide derivatives of 5-substituted-5,6,7,8-tetrahydro-1,7-naphthyridine-3-hydroxamates



vii **x** **xi**

[00147] Reaction of the secondary amine in compounds represented by **vii** with sulfonyl chlorides (R^3-SO_2Cl; Method J) leads to the formation of the corresponding sulfonamides **x**. Conversion of **x** to its corresponding hydroxamate is carried out in an analogous fashion as shown in Scheme 2 (Method I) leading to the formation of compounds of formula **xi**. Carbamate derivatives can also be prepared in a similar fashion by the use of the appropriate chloroformate (R^3-COOCl).

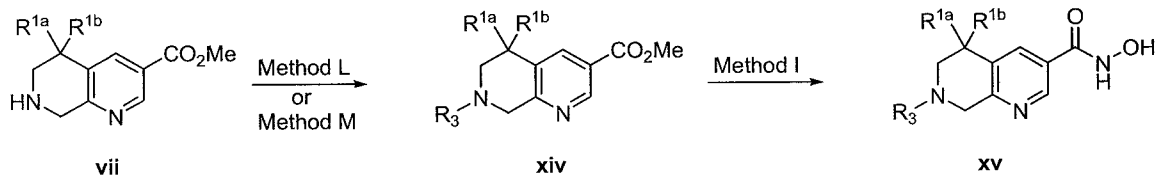
Scheme 4: General method for the preparation of urea derivatives of 5-substituted-5,6,7,8-tetrahydro-1,7-naphthyridine-3-hydroxamates



vii **xii** **xiii**

[00148] The reaction of compounds of formula **vii** with isocyanates (R^3-NCO; Method K) leads to the formation of the corresponding ureas of formula **xii**. Conversion of **xii** to the corresponding hydroxamates is carried out in an analogous fashions as shown in Scheme 2 (Method I) leading to the formation of compounds of formula **xiii.**

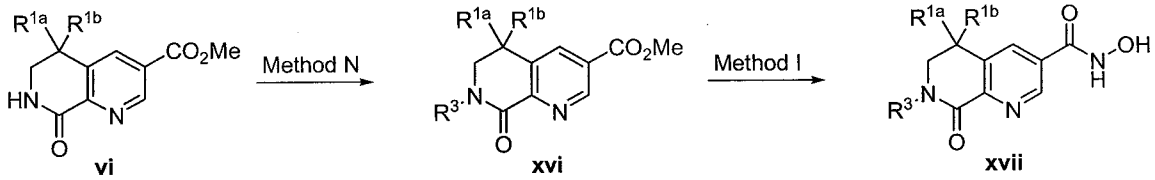
Scheme 5: General method for the preparation of N-aryl or N-alkyl derivatives of 5-substituted-5,6,7,8-tetrahydro-1,7-naphthyridine-3-hydroxamates



vii **xiv** **xv**

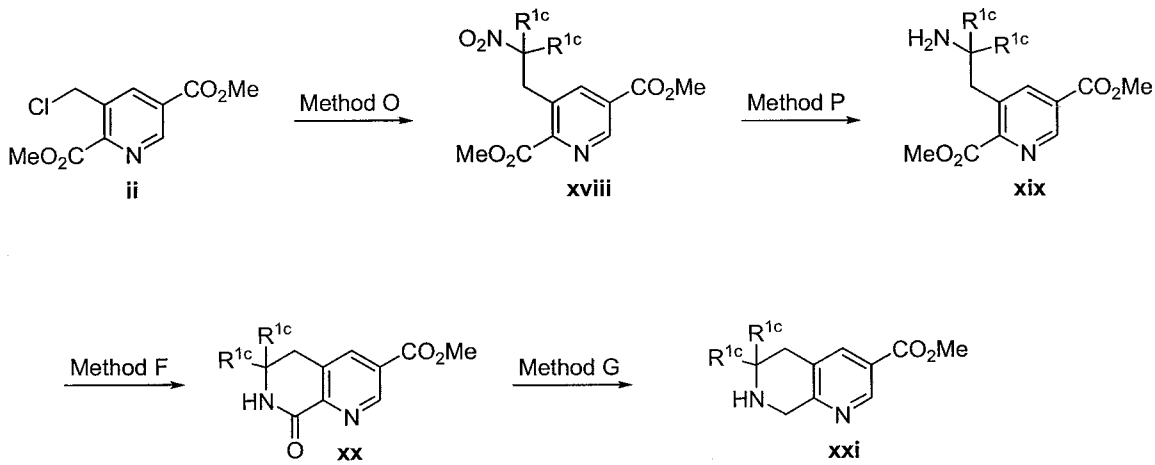
[00149] The generation of N-alkyl or N-aryl derivatives of 5-substituted-5,6,7,8-tetrahydro-1,7-naphthyridine-3-hydroxamates as depicted by formula **xv** is shown in Scheme 5. Treatment of compounds **vii** with alkyl halides in the presence of a base such as potassium carbonate (Method L) or reductive alkylations with ketones or aldehydes employing reducing agents such as sodium triacetoxyborohydride (Method M) provides tertiary amines of formula **xiv**. Compounds of formula **xiv** where R^3 is aryl may also be generated from compounds of formula **vii** by palladium-mediated Buchwald type couplings. Conversion of **xiv** to the corresponding hydroxamate is carried out in an analogous fashion to that shown in Scheme 2 (Method I) leading to the formation of compounds of formula **xv**.

Scheme 6: General method for the preparation of 7-alkyl derivatives of 5-sustituted-8-oxo-5,6,7,8-tetrahydro-1,7-naphthyridine-3-hydroxamates



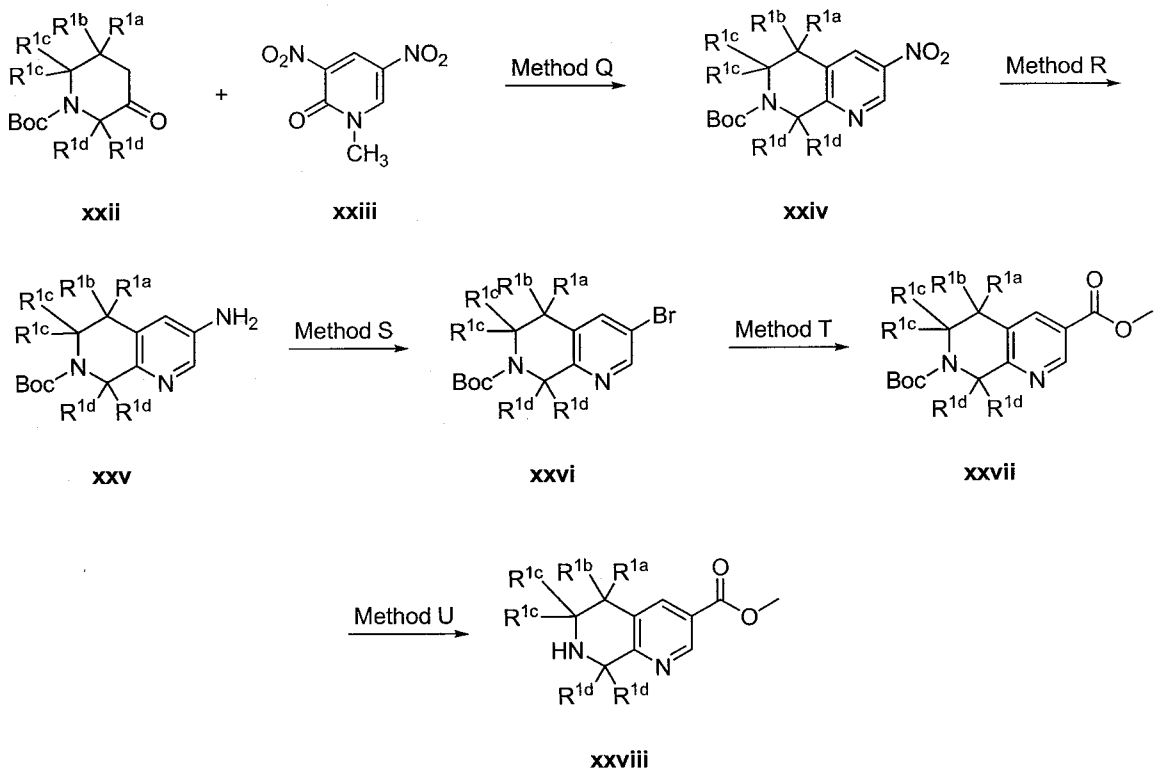
[00150] Scheme 6 above depicts a general method for the formation of 7-alkyl derivatives of 5-sustituted-8-oxo-5,6,7,8-tetrahydro-1,7-naphthyridine-3-hydroxamates represented by **xvii**. Initial deprotonation of the lactam **vi** upon treatment with sodium hydride at reduced temperatures followed by alkylation with alkyl halides (Method N; Jin *et al., Bioorg. Med. Chem. Lett.* **2009**, 19(8):2263) affords compounds of formula **xvi**. Conversion of **xvi** to the corresponding hydroxamate is carried out in an analogous fashions to that shown in Scheme 2 (Method I) leading to the formation of compounds of formula **xvii.**

Scheme 7: General method for the preparation of 6 substituted methyl 5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxylates



[00151] Substitutions at the 6-position of methyl 5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxylates may be carried out as depicted in Scheme 7. The reactive species resulting from deprotonation of a nitroalkane such as 2-nitropropane can displace the benzylic halide (Method O) of **ii** to give compounds represented by formula **xviii**. Reduction of the nitro function employing methods such as catalytic hydrogenation (Method P) to give compounds of formula **xix** followed by cyclization in the presence of base (Method F as described in Scheme 1) forms lactams of formula **xx**. Reduction of the lactam gives the corresponding secondary amine of formula **xxi** (Method G). It will be appreciated that compounds of the type **xx** and **xxi** can be further functionalized in a similar fashion to that depicted in Schemes 2-6.

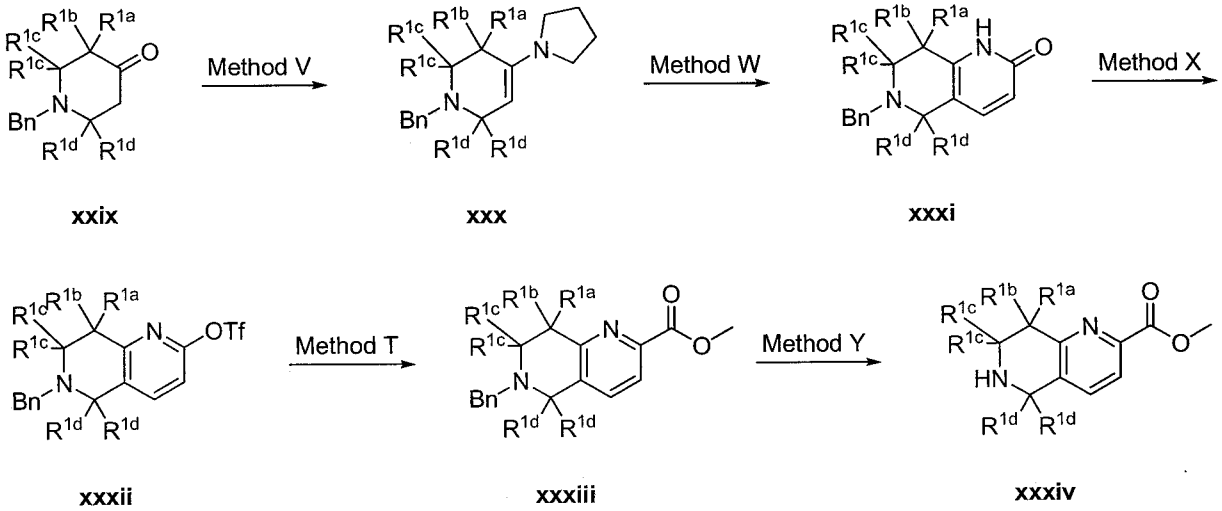
Scheme 8: General method for the preparation of substituted methyl 5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxylates



[00152] Scheme 8 depicts a complimentary route to Schemes 1 and 7 for construction of the substituted tetrahydronaphthyridine system. Condensation of 1-methyl-3,5-dinitro-2-pyridone **xxiii** with carbamate protected piperdones **xxii** (accessible either via reported literature methods or via commercial sources) under microwave irradiation provides the 5-nitropyridine compound of formula **xxiv** (Method Q; Henry *et al., J. Org. Chem.* **2009**, 74(5):1932). Reduction of the nitro group employing any of a variety of methods known to those skilled in the art gives anilines **xxv** (Method R). Conversion of **xxv** to the bromide employing sodium nitrite or an organic nitrite derivative such as *t*-butyl nitrite in the presence of

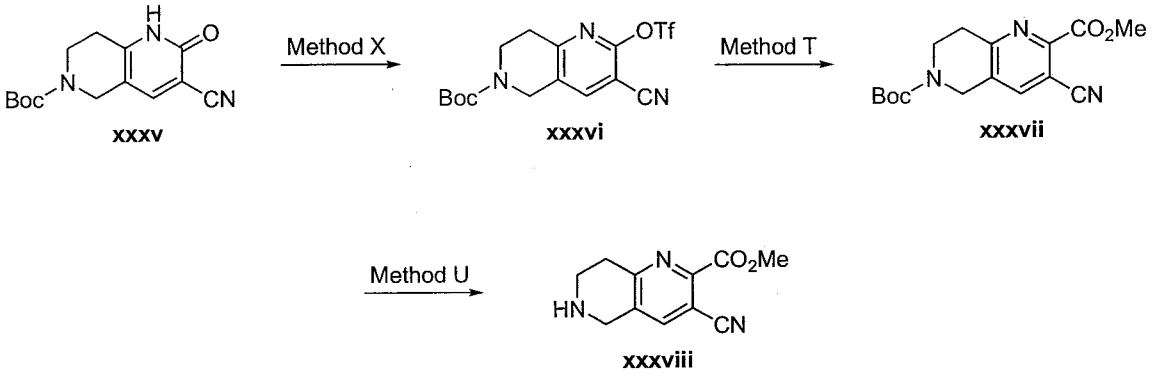
copper (II) bromide (Sandmeyer reaction) generates compounds of formula **xxvi** (Method S; Afonso *et al.*, *Biorg. Med. Chem.* **1999**, 7(9):1845). The newly installed bromide may be carbonylated in the presence of carbon monoxide gas, methanol and a suitable palladium catalyst and ligand (Method T; Buchwald *et al.*, *J. Org. Chem.*, **2008** 73:7102) to afford the methyl ester **xxvii**. Boc deprotection is carried out in the presence of a suitable acid such as HCl (Method Q) to afford the desired amine of formula **xxviii**. It will be appreciated that compounds of the type **xxviii** can then be further functionalized in a similar fashion to that depicted in Schemes 2-5.

Scheme 9: General method for the preparation of substituted methyl 5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylates



[00153] The condensation of compounds of formula **xxix**, which are either comerically available or known in the literature, with pyrrolidine along with azeotropic removal of water employing Dean Stark conditions provides enamines **xxx** (Method V; Berlin *et al.*, Intl. App. Pub. No. WO 91/07405). Reaction of **xxx** with excess propiolamide at elevated temperatures in a suitable solvent such as toluene, ethanol, xylene or tetrahydrofuran provides access to **xxxi** (Method W; Strang *et al.*, EP 1595881). Treatment of the pyridone **xxxi** with 1,1,1-trifluoromethanesulfonanilide in the presence of hindered nitrogen bases in an appropriate solvent with heating provides triflate **xxxii**. (Method Y; Carruthers *et al.*, U.S. App. Pub. No. 2005/0222151). The installation of the methyl ester is accomplished *via* carbonylation of compound **xxxii** in a similar fashion to that outlined in Scheme 8 (Method T). Cleavage of the benzyl protecting group to give compounds of formula **xxxiv** is achieved by catalytic hydrogenolysis employing standard methodology as described in "Protective Groups in Organic Synthesis", T. Greene and P. Wuts, 4th edition, 2007, John Wiley and Sons (Method Y). It will be appreciated that compounds of the type **xxxiv** can be further functionalized in a similar fashion to that depicted in Schemes 2-5.

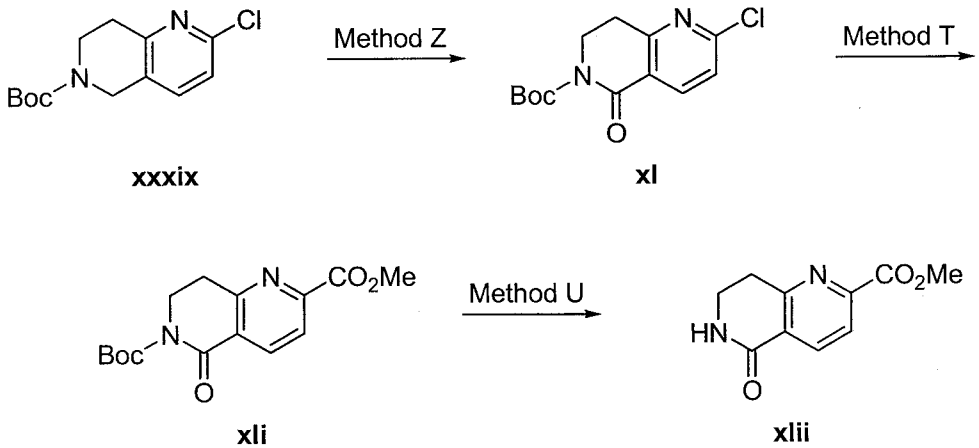
Scheme 10: General method for the preparation of methyl 3-cyano-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate



xxxv xxxvi xxxvii xxxviii

[00154] Scheme 10 depicts a route for the preparation of compounds of formula **xxxviii**. The pyridone **xxxv** (prepared as described by Davenport *et al.*, Intl. App. Pub. No.WO 09/121812) can be converted to the corresponding trfilate **xxxvi** upon treatment with 1,1,1-trifluoromethanesulfonanilide (Method X; see Scheme 9). Carbonylation (Method T; see Scheme 9) to generate **xxxvii** followed by removal of the Boc protecting group (Method U; see Scheme 8) affords **xxxviii**. It will be appreciated that compounds of formula **xxxviii** can be further functionalized in a similar fashion to that depicted in Schemes 2-5. It will also be appreciated that analogous sequences can be carried out with other suitably substituted analogs leading to compounds of formula **xxxviii** with additional substitution on either ring.

Scheme 11: General method for the preparation of methyl 5-oxo-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate

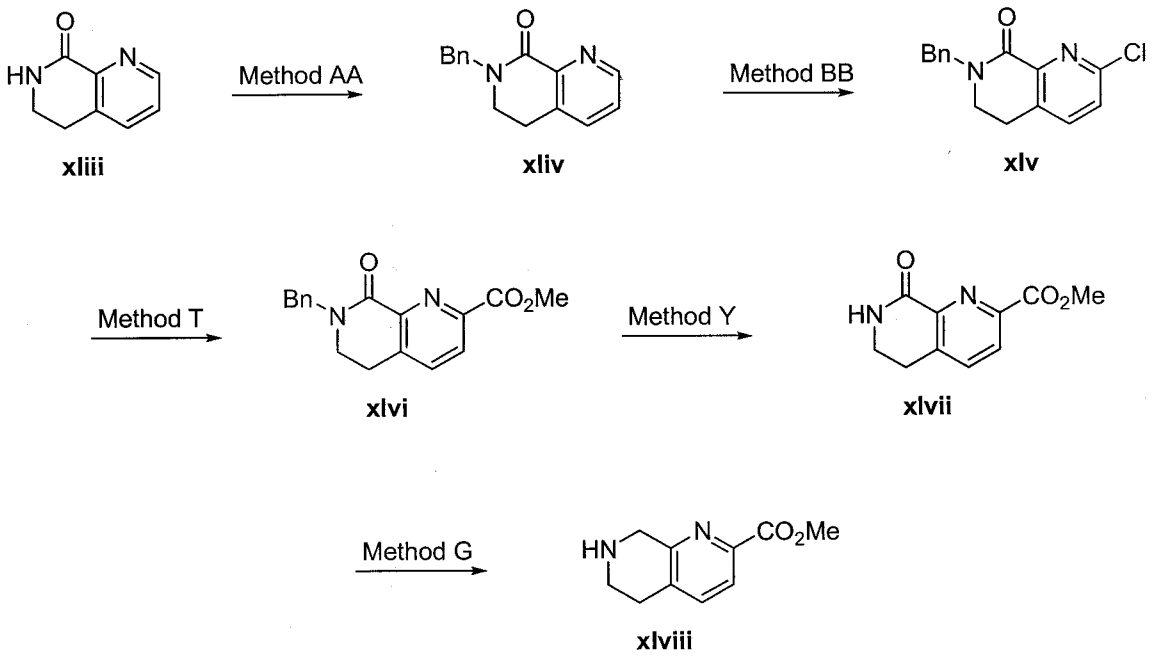


xxxix xl xli xlii

[00155] Scheme 11 shows a general route for the synthesis of methyl 5-oxo-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate **xlii**. Oxidation of commercially available **xxxix** with $NaIO_4$ and RuO_2 (Method Z; Davenport *et al.*, Intl. App. Pub. No. WO 09/121812) provides lactam **xl**. Carbonylation

(Method T; see Scheme 9) to generate **xli** followed by removal of the Boc protecting group (Method U; see Scheme 8) affords **xlii**. It will be appreciated that compound **xlii** can be further functionalized in a similar fashion as depicted in Scheme 6. It will also be appreciated that analogous sequences can be carried out with other suitably substituted analogs leading to compounds of formula **xlii** with additional substitution on either ring.

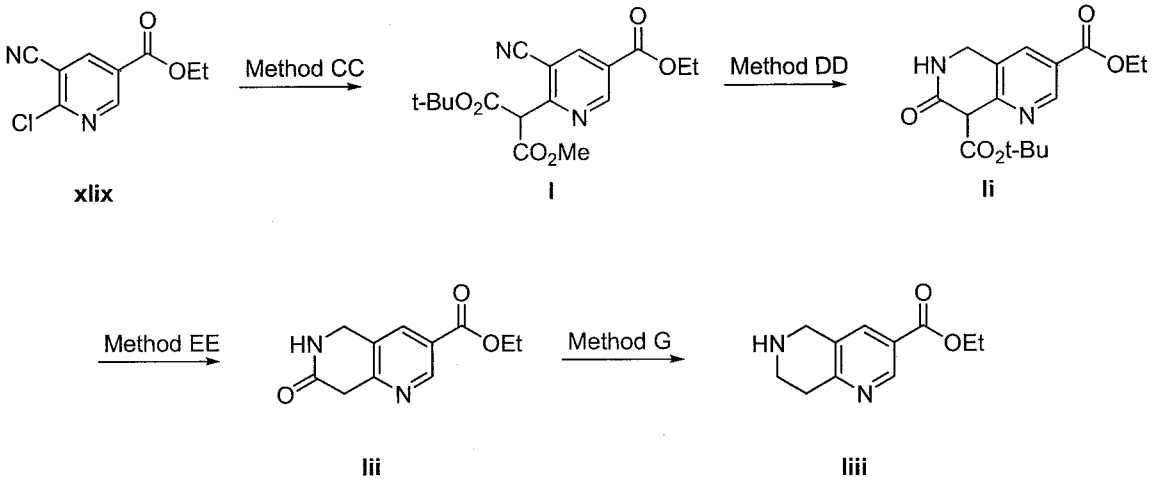
Scheme 12: General method for the preparation of methyl 5,6,7,8-tetrahydro-1,7-naphthyridine-2-carboxylate



xliii **xliv** **xlv** **xlvi** **xlvii** **xlviii**

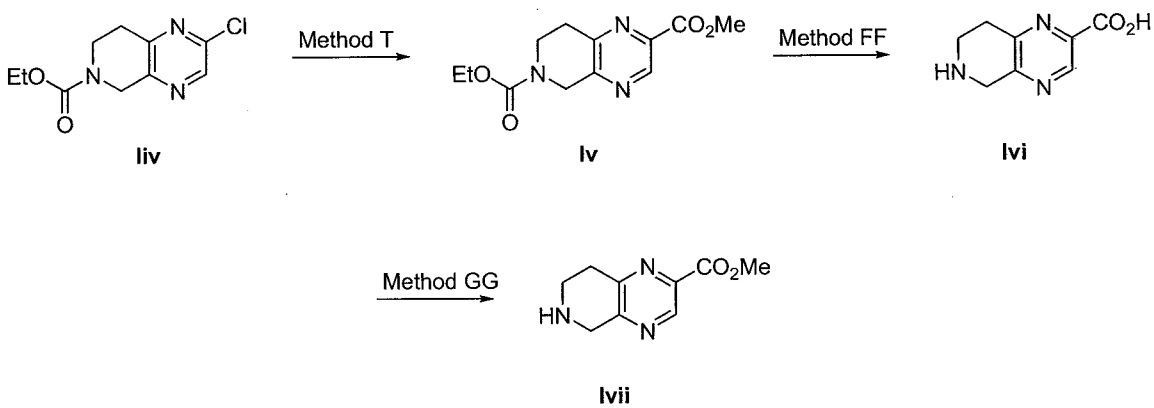
[00156] Scheme 12 depicts a general route for the preparation methyl 5,6,7,8-tetrahydro-1,7-naphthyridine-2-carboxylate as represented by **xlviii**. Treatment of the lactam **xliii** (prepared as described by Davenport *et al.*, Intl. App. Pub. No.WO 10/052222) with sodium hydride in an appropriate solvent followed by the addition of benzyl bromide provides the corresponding tertiary amide **xliv**. Oxidation of **xliv** with 3-chloroperoxybenzoic acid (*m*-CPBA) affords the *N*-oxide derivative intermediate, which upon subsequent treatment with phosphorus oxychloride generates the 2-chloro substituted compound **xlv** (Method BB; Davenport *et al.*, Intl. App. Pub. No.WO 10/052222). Carbonylation (Method T; see Scheme 8), hydrogenation (Method Y; see Scheme 9) and reduction of the lactam carbonyl (Method G; see Scheme 1) provides compounds of formula **xlviii**. It should be appreciated that compounds of the type **xlvii** and **xlviii** can be further functionalized in a similar fashion to that shown in Schemes 2-6. It will also be appreciated that analogous sequences can be carried out with other suitably substituted analogs leading to compounds of formula **xlvii** and **xlviii** with additional substitution on either ring.

Scheme 13: General method for the preparation of ethyl 5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate



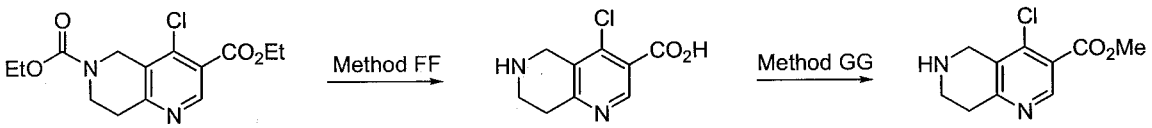
[00157] Scheme 13 shows a general method for the preparation of ethyl 5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylates of the general formulas **lii** and **liii**. Beginning with ethyl 6-chloro-5-cyanonicotinate **xlix** (prepared as described by Matasi *et al.*, Intl. App. Pub. No.WO 06/002051), displacement of the chloro group with the sodium salt of *t*-butyl methyl malonate (Method CC; Morgentin *et al.*, *Tetrahedron* **2009**, 65(4):757-764) to give compound **l** followed by reduction of the nitrile with hydrogen in the presence of catalytic Raney nickel causes cyclization afford compound **li** (Method DD; DeMartino *et al.*, U.S. App. Pub. No. 2006/0030582). Decarboxylation of the *t*-butyl ester of compound **li** in the presence of trifluoroacetic acid leads to the formation of **lii** (Method EE; DeMartino *et al.*, U.S. App. Pub. No. 2006/0030582). Removal of the lactam carbonyl is accomplished by similar means to that depicted in Scheme 1 (Method G) to afford **liii**. It will be appreciated that compounds of the type **lii** and **liii** can be further functionalized in a similar fashion to that shown in Schemes 2-6. It will also be appreciated that analogous sequences can be carried out with other suitably substituted analogs leading to compounds of formula **lii** and **liii** with additional substitution on the aromatic ring.

Scheme 14: General method for the preparation of methyl 5,6,7,8-tetrahydropyrido[3,4-b]pyrazine-2-carboxylate



[00158] Scheme 14 depicts a synthetic route to the preparation of compounds of formula **lvii**. Carbonylation of **liv** (prepared as described by Gao *et al.*, Intl. App. Pub. No.WO 07/106349) (Method T; see Scheme 8) affords the methyl ester containing compound **lv**. Exhaustive hydrolysis of both the carbamate and ester with KOH in an appropriate solvent with heat (Method FF; Gao *et al.*, Intl. App. Pub. No. WO 07/106349) leads to compound **lvi**. Fischer esterification of **lvi** in an alcoholic solvent with catalytic acid and heat (Method GG) provides compound **lvii**. It will be appreciated that compound **lvii** can then be further functionalized in a similar fashion to that shown in Schemes 2-5. It will also be appreciated that analogous sequences can be carried out with other suitably substituted analogs leading to compounds of formula **lvii** with additional substitution on either ring.

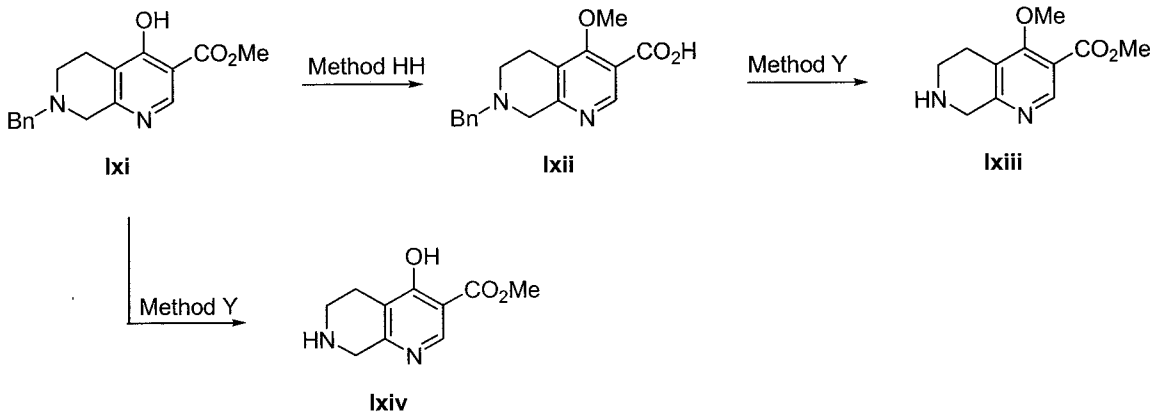
Scheme 15: General method for the preparation of methyl 4-chloro-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate



lviii **lix** **lx**

[00159] Scheme 15 depicts a route for the preparation of **lx**. Compound **lviii** (obtained as described by Mitchinson *et al.*, *Bioorg. Med. Chem. Lett.* **2004**, 14(13):3441–3444) can be hydrolyzed (Method FF; see Scheme 14) to give amino acid **lix**. Fischer esterification (Method GG) affords the amino ester **lx**. It will be appreciated that compound **lx** can then be further functionalized in a similar fashion to that shown in Schemes 2-5. It will also be appreciated that analogous sequences can be carried out with other suitably substituted analogs leading to compounds of formula **lx** with additional substitution on either ring.

Scheme 16: General method for the preparation of methyl 4-methoxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxylate and methyl 4-hydroxy-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxylate



lxi **lxii** **lxiii**

lxiv

[00160] Scheme 16 illustrates a synthetic route for access to compounds of formula **lxiii** and **lxiv**. Treatment of **lxi** (prepared as described previously by Kelly *et al.*, Intl. App. Pub. No.WO 06/102610) with diazomethane allows for methylation of the free hydroxy group to give **lxii** (Method HH, Ouali *et al.*, *Tetrahedron* **1980**, 36(12):1821). Removal of the benzyl group through hydrogenation (Method Y; see Scheme 9) affords **lxiii**. Alternatively, **lxii** can be hydrogenated (Method Y; see Scheme 9) directly to provide **lxiv.** It will be appreciated that compound **lxiii** and **lxiv** can then be further functionalized in a similar fashion to that shown in Schemes 2-5. It will also be appreciated that analogous sequences can be carried out with other suitably substituted analogs leading to compounds of formulas **lxiii** and **lxiv** with additional substitution on either ring.

5. Uses, Formulation and Administration

[00161] In another aspect, the present invention provides compounds of formulas (*I*), (*II*), (*III*), (*IV*), or their sub-formulas for used in medicine. As discussed above, the present invention provides compounds and pharmaceutical compositions that are useful as inhibitors of HDAC enzymes, particularly HDAC6, and thus the present invention provides compounds for use in treating proliferative, inflammatory, infectious, neurological or cardiovascular disorders.

[00162] The compounds and pharmaceutical compositions of the invention are particularly useful for the treatment of cancer. As used herein, the term "cancer" refers to a cellular disorder characterized by uncontrolled or disregulated cell proliferation, decreased cellular differentiation, inappropriate ability to invade surrounding tissue, and/or ability to establish new growth at ectopic sites. The term "cancer" includes, but is not limited to, solid tumors and bloodborne tumors. The term "cancer" encompasses diseases of skin, tissues, organs, bone, cartilage, blood, and vessels. The term "cancer" further encompasses primary and metastatic cancers.

[00163] In some embodiments, therefore, the invention provides the compound of formula (*I*), or a pharmaceutically acceptable salt thereof, for use in treating cancer. In some embodiments, the invention provides a pharmaceutical composition (as described herein) for the treatment of cancer comprising the compound of formula (*I*), or a pharmaceutically acceptable salt thereof. In some embodiments, the invention provides the use of the compound of formula (*I*), or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition (as described herein) for the treatment of cancer. In some embodiments, the invention provides the use of an effective amount of the compound of formula (*I*), or a pharmaceutically acceptable salt thereof, for the treatment of cancer.

[00164] Non-limiting examples of solid tumors that can be treated with the disclosed inhibitors include pancreatic cancer; bladder cancer; colorectal cancer; breast cancer, including metastatic breast cancer; prostate cancer, including androgen-dependent and androgen-independent prostate cancer; renal cancer, including, e.g., metastatic renal cell carcinoma; hepatocellular cancer; lung cancer, including, e.g.,

non-small cell lung cancer (NSCLC), bronchioloalveolar carcinoma (BAC), and adenocarcinoma of the lung; ovarian cancer, including, e.g., progressive epithelial or primary peritoneal cancer; cervical cancer; gastric cancer; esophageal cancer; head and neck cancer, including, e.g., squamous cell carcinoma of the head and neck; melanoma; neuroendocrine cancer, including metastatic neuroendocrine tumors; brain tumors, including, e.g., glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma; bone cancer; and soft tissue sarcoma.

[00165] Non-limiting examples of hematologic malignancies that can be treated with the disclosed inhibitors include acute myeloid leukemia (AML); chronic myelogenous leukemia (CML), including accelerated CML and CML blast phase (CML-BP); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkin's disease (HD); non-Hodgkin's lymphoma (NHL), including follicular lymphoma and mantle cell lymphoma; B-cell lymphoma; T-cell lymphoma; multiple myeloma (MM); Waldenstrom's macroglobulinemia; myelodysplastic syndromes (MDS), including refractory anemia (RA), refractory anemia with ringed siderblasts (RARS), (refractory anemia with excess blasts (RAEB), and RAEB in transformation (RAEB-T); and myeloproliferative syndromes.

[00166] In some embodiments, compounds of the invention are suitable for the treatment of breast cancer, lung cancer, ovarian cancer, multiple myeloma, acute myeloid leukemia or acute lymphoblastic leukemia.

[00167] In other embodiments, compounds of the invention are suitable for the treatment of inflammatory and cardiovascular disorders including, but not limited to, allergies/anaphylaxis, acute and chronic inflammation, rheumatoid arthritis; autoimmunity disorders, thrombosis, hypertension, cardiac hypertrophy, and heart failure.

[00168] Accordingly, in another aspect of the present invention, pharmaceutical compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00169] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00170] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, 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. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of HDAC6.

[00171] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, *66*, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00172] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used

in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00173] In yet another aspect, a method for treating a proliferative, inflammatory, infectious, neurological or cardiovascular disorder is provided comprising administering an effective amount of a compound, or a pharmaceutical composition to a subject in need thereof. In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutical composition is that amount effective for treating a proliferative, inflammatory, infectious, neurological or cardiovascular disorder, or is that amount effective for treating cancer. In other embodiments, an “effective amount” of a compound is an amount which inhibits binding of HDAC6, and thereby blocks the resulting signaling cascades that lead to the abnormal activity of growth factors, receptor tyrosine kinases, protein serine/threonine kinases, G protein coupled receptors and phospholipid kinases and phosphatases.

[00174] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating the disease. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and

the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disease being treated and the severity of the disease; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00175] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00176] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, 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, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00177] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a

solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00178] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00179] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00180] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00181] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00182] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00183] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00184] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00185] In some embodiments, a compound of formula (*I*) or a pharmaceutical composition thereof is administered in conjunction with an anticancer agent. As used herein, the term "anticancer agent" refers to any agent that is administered to a subject with cancer for purposes of treating the cancer.

Combination therapy includes administration of the therapeutic agents concurrently or sequentially. Alternatively, the therapeutic agents can be combined into one composition which is administered to the patient.

[00186] Non-limiting examples of DNA damaging chemotherapeutic agents include topoisomerase I inhibitors (e.g., irinotecan, topotecan, camptothecin and analogs or metabolites thereof, and doxorubicin); topoisomerase II inhibitors (e.g., etoposide, teniposide, and daunorubicin); alkylating agents (e.g., melphalan, chlorambucil, busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, decarbazine, methotrexate, mitomycin C, and cyclophosphamide); DNA intercalators (e.g., cisplatin, oxaliplatin, and carboplatin); DNA intercalators and free radical generators such as bleomycin; and nucleoside mimetics (e.g., 5-fluorouracil, capecitibine, gemcitabine, fludarabine, cytarabine, mercaptopurine, thioguanine, pentostatin, and hydroxyurea).

[00187] Chemotherapeutic agents that disrupt cell replication include: paclitaxel, docetaxel, and related analogs; vincristine, vinblastin, and related analogs; thalidomide, lenalidomide, and related analogs (e.g., CC-5013 and CC-4047); protein tyrosine kinase inhibitors (e.g., imatinib mesylate and gefitinib); proteasome inhibitors (e.g., bortezomib); NF-κB inhibitors, including inhibitors of IκB kinase; antibodies which bind to proteins overexpressed in cancers and thereby downregulate cell replication (e.g., trastuzumab, rituximab, cetuximab, and bevacizumab); and other inhibitors of proteins or enzymes known to be upregulated, over-expressed or activated in cancers, the inhibition of which downregulates cell replication. In certain embodiments, a compound of the invention is administered in conjunction with a proteasome inhibitor.

[00188] Another aspect of the invention relates to inhibiting HDAC6, activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of formula (*I*), or a composition comprising said compound. The term "biological sample", as used herein, generally includes *in vivo*, *in vitro*, and *ex vivo* materials, and also includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00189] Still another aspect of this invention is to provide a kit comprising separate containers in a single package, wherein the inventive pharmaceutical compounds, compositions and/or salts thereof are used in combination with pharmaceutically acceptable carriers to treat disorders, symptoms and diseases where HDAC6 plays a role.

6. Preparation of Exemplary Compounds

EXPERIMENTAL PROCEDURES

[00190] Definitions

AIBN	azobisisobutyronitrile
ATP	adenosine triphosphate
DCE	dichloroethane
DCM	dichloromethane
DIPEA	diisopropylethyl amine
DMAP	4-dimethylaminopyridine
DMF	*N, N*-dimethylformamide
DMSO	dimethylsulfoxide
EDTA	ethylenediaminetetraacetic acid
EtOAc	ethyl acetate
EtOH	ethanol
FA	formic acid
FBS	fetal bovine serum
h	hours
HATU	*N, N, N', N'*-tetramethyl-*o*-(7-azabenzotriazole-1-yl)uronium hexafluorophosphate
HEPES	*N*-(2-hydroxyethyl)piperazine-*N'*-(2-ethanesulfonic acid)
HRMS	high resolution mass spectrum
IPA	isopropyl alcohol
LC-MS	liquid chromatography mass spectrum
m/z	mass to charge
MTBE	methyl tert-butyl ether
Me	methyl
MEM	minimum essential media
MeOH	methanol
min	minutes
MS	mass spectrum
MWI	microwave irradiation
NMM	*N*-methyl morpholine
PBS	phosphate buffered saline
rt	room temperature
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFFH	1,1,3,3-tetramethylfluoroformamidinium hexafluorophosphate

THF	tetrahydrofuran
TMEDA	*N*, *N*, *N'*, *N'*-tetramethyl-ethane-1,2-diamine
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

[00191] Analytical Methods

[00192] **NMR:** 1H NMR spectra are run on a 400 MHz Bruker unless otherwise stated.

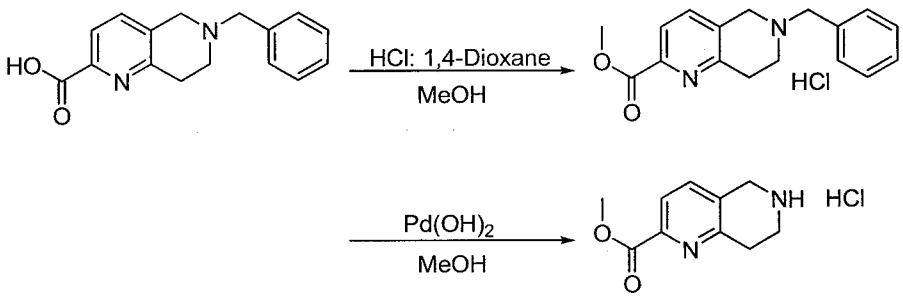
[00193] **LC-MS**: LC-MS spectra are run using an Agilent 1100 LC interfaced to a micromass Waters® Micromass® Zspray™ Mass Detector (ZMD) using the following gradients:

Formic Acid (FA): Acetonitrile containing zero to 100 percent 0.1% formic acid in water.

Ammonium Acetate (AA): Acetonitrile containing zero to 100 percent 10 mM ammonium acetate in water.

[00194] **HPLC**: Preparative HPLC are conducted using 18x150 mm Sunfire C-18 columns eluting with water-MeCN gradients using a Gilson instrument operated by 322 pumps with the UV/visible 155 detector triggered fraction collection set to between 200 nm and 400 nm. Mass gated fraction collection is conducted on an Agilent 1100 LC/MSD instrument.

Example 1: methyl 5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate hydrochloride



Step 1: methyl 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate hydrochloride

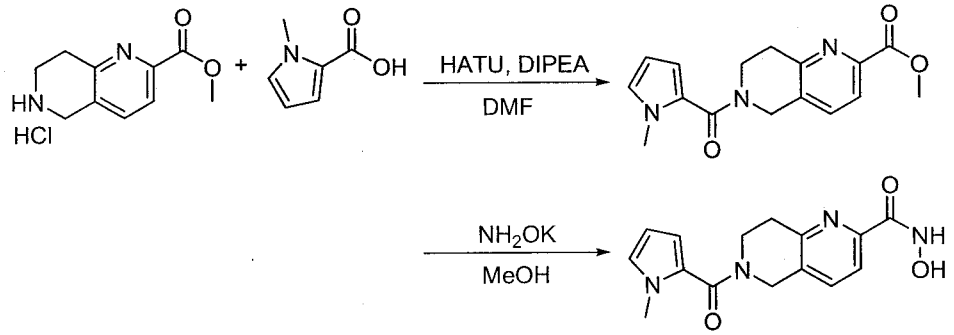
[00195] In a sealed container, 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylic acid (1.00 g, 3.73 mmol) was dissolved in MeOH (40.0 mL) and HCl (3.29 mL, 14.9 mmol, 4.0 M in 1,4-dioxane). The resulting solution was heated at 80 °C for 13 h. The solvent and acid were completely evaporated to yield methyl 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate hydrochloride (1.25 g, 100%). LC-MS: (FA) ES+ 283; ^{1}H NMR (Methanol-d_4, 400 MHz) δ8.08 (d, J = 8.0 Hz, 1 H), 7.92 (d, J = 8.3 Hz, 1 H), 7.63 (m, 2 H), 7.54 (m, 3 H), 4.88 (s, 2 H), 4.58 (s, 4 H), 3.99 (s, 3 H), 3.40 (s, 2 H).

Step 2: methyl 5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate hydrochloride

[00196] The crude methyl 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate hydrochloride (1.20 g, 3.76 mmol) was dissolved in MeOH (100 mL) and thoroughly degassed. Palladium hydroxide

(0.185 g, 1.32 mmol) was added to the solution before being purged with H_2 gas three times. The reaction was allowed to stir at rt for 13 h under 1 atm of H_2 gas. The mixture was then filtered through a pad of Celite and rinsed with EtOH. The filtrate was then concentrated down to yield methyl 5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate hydrochloride (0.97 g, 100%). LC-MS: (FA) ES+ 220; ^{1}H NMR (Methanol-d_4, 400 MHz) δ 8.05 (d, J = 8.0 Hz, 1 H), 7.89 (d, J = 8.0 Hz, 1 H), 4.52 (s, 2 H), 3.98 (s, 3 H), 3.66 (t, J = 6.5 Hz, 2 H), 3.33 (m, 2 H).

Example 2: *N*-hydroxy-2-(1-methyl-1*H*-pyrrole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide Compound I-11



Step 1: methyl 2-(1-methyl-1*H*-pyrrole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylate

[00197] To a vial containing *N*-methylpyrrole-2-carboxylic acid (0.0206 g, 0.165 mmol) was added HATU (0.0627 g, 0.165 mmol) in DMF (1.00 mL) followed by DIPEA (0.157 mL, 0.9 mmol) in DMF (0.5 mL). The mixture was shaken at rt for 30 min before methyl 5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate hydrochloride (0.0343 g, 0.15 mmol) in DMF (1.00 mL) was added. The solution was then shaken at rt for 13 h. The solvent was evaporated and to the residue was added DCE (3 mL), water (1 mL), and a few drops of ammonia in MeOH (7 *N*). After being thoroughly mixed, the layers were separated and the aqueous layer was extracted with DCE (3 mL). The combined organic phases were then concentrated to give a solid residue.

Step 2: *N*-hydroxy-2-(1-methyl-1*H*-pyrrole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide

[00198] Methyl 2-(1-methyl-1*H*-pyrrole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylate in a vial was dissolved in MeOH (1 mL) and hydroxylamine potassium salt (0.682 mL, 1.2 mmol; 1.76 M in MeOH) was added. The solution was shaken at rt for 2 h before acetic acid (0.0682 mL, 1.2 mmol) was added to neutralize the reaction. The solvent was then completely evaporated and to the residue was added DMSO (1.2 mL). After filtration, the solution was purified by prep-HPLC to yield *N*-hydroxy-2-(1-methyl-1*H*-pyrrole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide (0.0073 g, 16.2%). LC-MS: (AA) ES+ 301; ^{1}H NMR (Methanol-d_4, 400 MHz) δ 7.87 (d, J = 8.0 Hz, 1 H), 7.72 (d, J = 8.0 Hz, 1

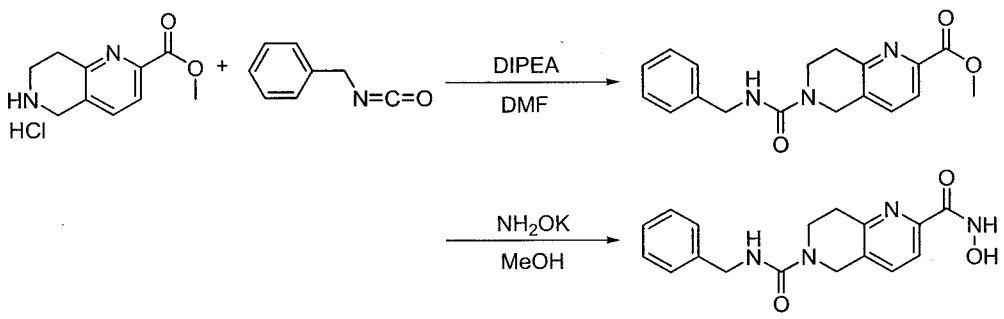
H), 6.86 (t, J = 1.8 Hz, 1 H), 6.52 (dd, J = 3.8, 1.5 Hz, 1 H), 6.12 (dd, J = 3.8, 2.5 Hz, 1 H), 4.96 (s, 2 H), 4.07 (t, J = 5.8 Hz, 2 H), 3.74 (s, 3 H), 3.11 (t, J = 6.0 Hz, 2 H).

Example 3

[00199] The compounds shown below were prepared in an analogous fashion to that described in Example 2 starting from the appropriate starting materials:

Compound No	LC-MS (FA)
I-6	ES+ 396
I-49	ES+ 354
I-33	ES+ 333
I-7	ES+ 413
I-22	ES+ 356
I-27	ES+ 319
I-14	ES+ 338
I-2	ES+ 236
I-46	ES+ 278
I-19	ES+ 318
I-35	ES+ 328
I-38	ES+ 284

Example 4: N^6-benzyl-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide Compound I-25



Step 1: methyl 6-(benzylcarbamoyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate

[00200] To a vial containing benzyl isocyanate (0.0166 g, 0.125 mmol), was added methyl 5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate hydrochloride (0.0220 g, 0.0962 mmol), DIPEA (0.0586 mL,

0.337 mmol) and DMF (2 mL). The resulting solution was then shaken at rt for 13 h and then concentrated to give methyl 6-(benzylcarbamoyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate.

Step 2: N^6-benzyl-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide

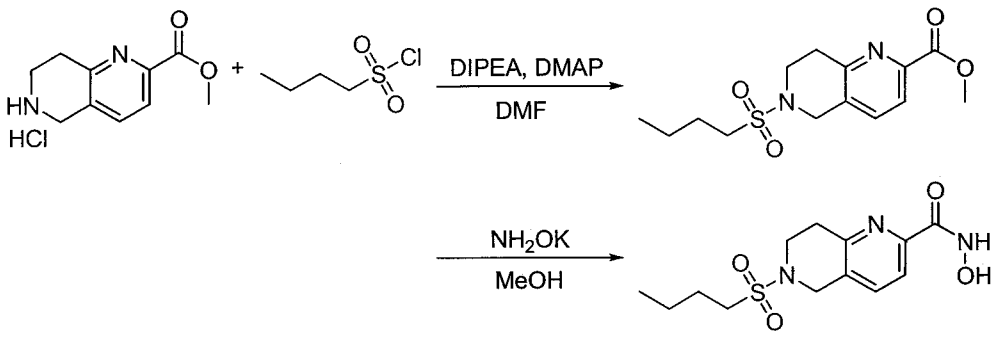
[00201] To a vial containing methyl 6-(benzylcarbamoyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate was added MeOH (1 mL) and hydroxylamine potassium salt (1 mL, 1.76 mmol, 1.76 M in MeOH) and the resulting mixture was shaken at rt for 13 h. The solution was quenched with acetic acid (0.200 mL, 3.52 mmol) before being concentrated. To the resulting residue was added DMSO (1.2 mL) and it was purified *via* prep-HPLC to yield N^6-benzyl-N^2-hydroxy-7,8-dihydro-1,6-naphthyridine-2,6(5*H*)-dicarboxamide (0.0113 g, 36.0%). LC-MS: (FA) ES+ 327; ^{1}H NMR (Methanol-d_4, 400 MHz) δ 7.86 (d, J = 7.8 Hz, 1 H), 7.70 (d, J = 8.0 Hz, 1 H), 7.25-7.19 (m, 5 H), 4.68 (s, 2 H), 4.39 (s, 2 H), 3.79 (t, J = 6.0 Hz, 2 H), 3.03 (t, J = 6.0 Hz, 2 H).

Example 5

[00202] The compounds shown below were prepared in an analogous fashion to that described in Example 4 starting from the appropriate starting materials:

Compound No	LC-MS (FA)
I-45	ES+ 293
I-43	ES+ 394
I-40	ES+ 369
I-51	ES+ 313
I-17	ES+ 319
I-13	ES+ 371
I-34	ES+ 389
I-8	ES+ 327
I-54	ES+ 395
I-55	ES+ 341
I-36	ES+ 279
I-47	ES+ 369
I-16	ES+ 293

Example 6: 6-(butylsulfonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide Compound I-61



Step 1: methyl 6-(butylsulfonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate

[00203] To a microwave vial containing *n*-butanesulfonyl chloride (0.0352 g, 0.225 mmol), was added methyl 5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate hydrochloride (0.0288 g, 0.15 mmol), TEA (0.167 mL, 1.2 mmol), DMAP (1.83 mg, 0.015 mmol), and DMF (2 mL). The mixture was shaken at rt for 13 h. The solvent was then completely evaporated to yield a solid. LC-MS: (FA) ES+ 313.

Step 2: 6-(butylsulfonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide

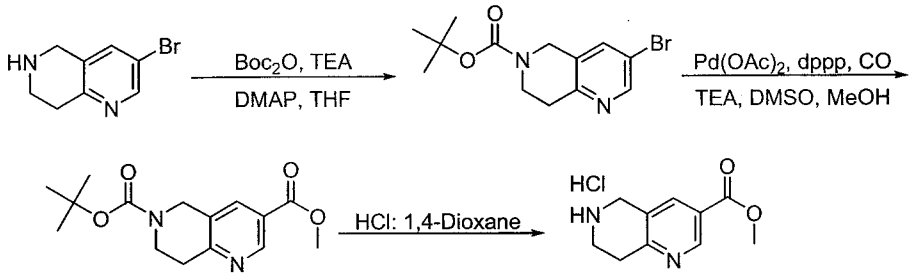
[00204] To a microwave vial containing methyl 6-(butylsulfonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate was added MeOH (1 mL) and hydroxylamine potassium salt (1 mL, 1.76 mmol, 1.76 M in MeOH). The solution was shaken at rt for 1 h, then acetic acid (0.102 mL, 1.8 mmol) was added to quench excess base. The solvent was then concentrated. To the resulting residue was added DMSO (1.2 mL) and after filtration, the solution underwent purification *via* prep-HPLC to give 6-(butylsulfonyl)-*N*-hydroxy-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxamide (13.3 mg, 28.3%). LC-MS: (FA) ES+ 314; ^{1}H NMR (Methanol-d_4, 300 MHz) δ 7.97 (d, J = 8.1 Hz, 1 H), 7.76 (d, J = 7.9 Hz, 1 H), 4.59 (s, 2 H), 3.70 (t, J = 6.0 Hz, 2 H), 3.13 (m, 4 H), 1.77 (m, 2 H), 1.47 (m, 2 H), 0.95 (t, J = 7.3 Hz, 3 H).

Example 7

[00205] The compounds shown below were prepared in an analogous fashion to that described in Example 6 starting from the appropriate starting materials:

Compound No	LC-MS (FA)
I-60	ES+ 406
I-59	ES+ 402

Example 8: methyl 5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate hydrochloride



Step 1: t-butyl 3-bromo-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate

[00206] To a flask containing 3-bromo-5,6,7,8-tetrahydro-1,6-naphthyridine (1.50 g, 7.04 mmol), was added THF (70 mL, 863 mmol), di-tert-butyldicarbonate (1.77 g, 8.10 mmol), TEA (5.89 mL, 42.2 mmol), and DMAP (43.0 mg, 0.352 mmol). The solution was stirred at rt for 4 h. The solvent was then concentrated. To the resulting residue was added EtOAc (150 mL) and water (50 mL). After separation, the aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic layers were then washed with water (2 × 100 mL), brine (100 mL), dried (Mg_2SO_4), and concentrated to yield *tert*-butyl 3-bromo-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (2.15 g, 97.5%). LC-MS: (FA) ES+ 314; ^{1}H NMR (Methanol-d_4, 300 MHz) δ8.43 (s, 1 H, 7.83 (s, 1 H), 4.60 (s, 2 H), 3.73 (t, J = 6.0 Hz, 2 H), 2.89 (t, J = 6.0 Hz, 2 H), 1.48 (s, 9 H).

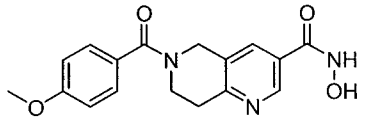
Step 2: 6-t-butyl 3-methyl 7,8-dihydro-1,6-naphthyridine-3,6(5*H*)-dicarboxylate

[00207] A solution of *tert*-butyl 3-bromo-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (2.15 g, 6.86 mmol), TEA (9.57 mL, 68.7 mmol), MeOH (25 mL) and DMSO (12.4 mL) was thoroughly degassed with N_2 gas for 15 min. Then 1,3-bis(diphenylphosphino)propane (0.442 g, 1.07 mmol) and palladium(II)acetate (0.240 g, 1.07 mmol) were quickly added to the solution. After purging the solution twice with CO gas, the solution was left to stir at 80 °C for 6 h under 1 atm of CO. MeOH was concentrated before EtOAc (400 mL) and water (100 mL) were added to the remaining DMSO residue. After separation, the aqueous phases were extracted with EtOAc (2 × 300 mL). Then combined organic phases were then washed with brine (100 mL), 1 *N* HCl (100 mL), dried ($MgSO_4$), and concentrated. Purification *via* flash column chromatography (EtOAc: hexanes, 1:4 to 1:1) afforded a yellow solid (1.79 g, 89.2%). LC-MS: (FA) ES+ 293; ^{1}H NMR ($CDCl_3$, 400 MHz) δ9.02 (s, 1 H), 8.03 (s, 1 H), 4.64 (s, 2 H), 3.95 (s, 3 H), 3.77 (t, J = 6.0 Hz, 2 H), 3.07 (t, J = 6.0 Hz, 2 H), 1.50 (s, 9 H).

Step 3: methyl 5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate hydrochloride

[00208] To a flask was added 6-*tert*-butyl 3-methyl 7,8-dihydro-1,6-naphthyridine-3,6(5*H*)-dicarboxylate (1.79 g, 6.12 mmol) and hydrochloric acid (23.0 mL, 91.8 mmol, 4.0 M in 1,4-dioxane). The mixture was stirred at rt for 1 h. The solvent was completely evaporated to yield methyl 5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate hydrochloride (1.64 g, 100%). LC-MS: (FA) ES+ 193.

Example 9: Synthesis of *N*-hydroxy-6-(4-methoxybenzoyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide Compound I-32



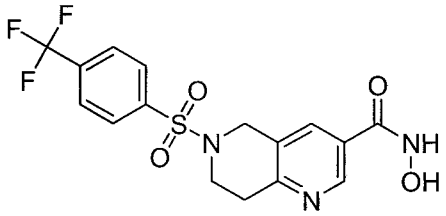
[00209] The title compound was prepared in an analogous fashion to that described in Example 2 starting from the appropriate starting materials. Yield: 36.9%. LC-MS (FA): ES+ 328; ^{1}H NMR (Methanol-d_4, 400 MHz) δ 8.72 (*s*, 1 H), 7.96 (*br*, 1 H), 7.47 (*d*, J = 8.8 Hz, 1 H), 7.03 (*d*, J = 8.8 Hz, 1 H), 4.86 (*s*, 2 H), 3.92 (*m*, 2 H), 3.84 (*s*, 3 H), 3.10 (*t*, J = 5.8 Hz, 2 H).

Example 10

[00210] The compounds below were prepared in an analogous fashion to that described in Example 2 starting from appropriate starting materials:

Compound No	LC-MS (FA)
I-20	ES+ 284
I-29	ES+ 413
I-50	ES+ 353
I-42	ES+ 381
I-39	ES+ 301
I-44	ES+ 338
I-53	ES+ 374
I-5	ES+ 389
I-56	ES+ 318
I-52	ES+ 354
I-31	ES+ 356
I-12	ES+333
I-1	ES+ 319
I-23	ES+ 396
I-30	ES+ 278

Example 11: *N*-hydroxy-6-(4-(trifluoromethyl)phenylsulfonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxamide Compound I-62



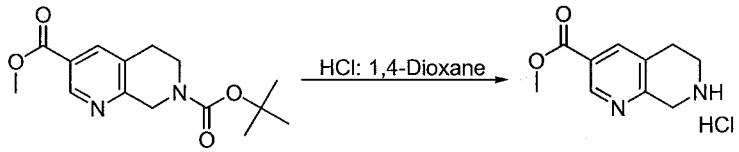
[00211] The title compound was prepared in an analogous fashion to that described in Example 6 starting from the appropriate starting materials. Yield: 66.2%. LC-MS (FA): ES+ 402; ^{1}H NMR (Methanol-d_4, 300 MHz) δ8.66 (s, 1 H), 8.08 (d, J = 8.1 Hz, 2 H), 7.92 (m, 3 H), 4.43 (s, 2 H), 3.58 (t, J = 6.0 Hz, 2 H), 3.05 (t, J = 6.0 Hz, 2 H).

Example 12

[00212] The compounds below were prepared in an analogous fashion to that described in Example 6 starting from the appropriate starting materials:

Compound No	LC-MS (FA)
I-57	ES+ 406
I-58	ES+ 314

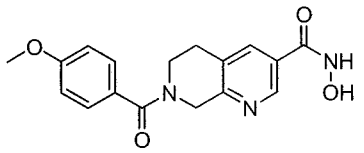
Example 13: methyl 5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate hydrochloride



Step 1: methyl 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carboxylate hydrochloride

[00213] A round-bottom flask containing 7-tert-butyl 3-methyl 5,6-dihydro-1,7-naphthyridine-3,7-(8*H*)-dicarboxylate (0.470 g, 1.61 mmol) and hydrochloric acid (6.03 mL, 24.1 mmol, 4.0 M in 1,4-dioxane) was stirred at rt for 1 h. The solution was then completely evaporated to yield methyl 5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxylate hydrochloride (0.440 g, 100%). LC-MS: (FA) ES+ 193; ^{1}H NMR (Methanol-d_4, 400 MHz) δ9.26 (s, 1 H), 8.87 (s, 1 H), 4.83 (s, 2 H), 4.03 (s, 3 H), 3.69 (m, 2 H), 3.43 (t, J = 5.5 Hz, 2 H).

Example 14: *N*-hydroxy-7-(4-methoxybenzoyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide Compound I-48



[00214] The title compound was prepared in an analogous fashion to that described in Example 2 starting from the appropriate starting materials. Yield: 29.3%. LC-MS (FA): ES+ 328; ^{1}H NMR (Methanol-d_4, 400 MHz) δ 8.70 (*s*, 1 H), 7.99 (*s*, 1 H), 7.47 (*d*, J = 8.8 Hz, 1 H), 7.02 (*d*, J = 8.8 Hz, 1 H), 4.86 (*s*, 2 H), 3.86 (*m*, 2 H), 3.84 (*s*, 3 H), 3.02 (*t*, J = 5.6 Hz, 2 H).

Example 15

[00215] The compounds below were prepared in an analogous fashion to that described in Example 2 starting from appropriate starting materials:

Compound No	LC-MS (FA)
I-28	ES+ 333
I-21	ES+236
I-10	ES+319
I-15	ES+356
I-41	ES+ 354
I-37	ES+ 413
I-4	ES+ 354
I-9	ES+ 318
I-18	ES+ 338
I-24	ES+ 301
I-3	ES+ 294

Example 16: HDAC6 enzyme assay

[00216] To measure the inhibition of HDAC6 activity, purified human HDAC6 (BPS Bioscience; Cat. No. 5006) is incubated with substrate Ac-Arg-Gly-Lys(Ac)-AMC peptide (Bachem Biosciences; Cat. No. I-1925) for 1 hour at 30 °C in the presence of test compounds or vehicle DMSO control. The reaction is stopped with the HDAC inhibitor trichostatin A (Sigma; Cat. No. T8552) and the amount of Arg-Gly-Lys-AMC generated is quantitated by digestion with trypsin (Sigma; Cat. No. T1426) and subsequent measurement of the amount of AMC released using a fluorescent plate reader (Pherastar; BMG

Technologies) set at Ex 340nm and Em 460nm. Concentration response curves are generated by calculating the fluorescence increase in test compound-treated samples relative to DMSO-treated controls, and percentage inhibition values at a single concentration or enzyme inhibition (IC_{50}) values are determined from those curves. One skilled in the art will appreciate that the values generated either as percentage inhibition at a single concentration or IC_{50} values are subject to experimental variation.

Example 17: Nuclear extract HDAC assay

[00217] As a screen against Class I HDAC enzymes, HeLa nuclear extract (BIOMOL; Cat. No. KI-140) is incubated with Ac-Arg-Gly-Lys(Ac)-AMC peptide (Bachem Biosciences; Cat. No. I-1925) in the presence of test compounds or vehicle DMSO control. The HeLa nuclear extract is enriched for Class I enzymes HDAC1, -2 and -3. The reaction is stopped with the HDAC inhibitor Trichostatin A (Sigma; Cat. No. T8552) and the amount of Arg-Gly-Lys-AMC generated is quantitated by digestion with trypsin (Sigma; Cat. No. T1426) and subsequent measurement of the amount of AMC released using a fluorescent plate reader (Pherastar; BMG Technologies) set at Ex 340nm and Em 460nm. Concentration response curves are generated by calculating the fluorescence increase in test compound-treated samples relative to DMSO-treated controls, and enzyme inhibition (IC_{50}) values are determined from those curves.

Example 18: Western Blot and Immunofluorescence Assays

[00218] Cellular potency and selectivity of compounds are determined using a published assay (Haggarty *et al.*, *Proc. Natl. Acad. Sci. USA* **2003**, 100 (8): 4389-4394) using Hela cells (ATCC cat# CCL-2™) which are maintained in MEM medium (Invitrogen) supplemented with 10% FBS; or multiple myeloma cells RPMI-8226 (ATCC cat# CCL-155™) which are maintained in RPMI 1640 medium (Invitrogen) supplemented with 10% FBS. Briefly, cells are treated with inhibitors for 6 or 24 h and either lysed for Western blotting, or fixed for immunofluorescence analyses. HDAC6 potency is determined by measuring K40 hyperacetylation of alpha-tubulin with an acetylation selective monoclonal antibody (Sigma cat# T7451) in IC50 experiments. Selectivity against Class I HDAC activity is determined similarly using an antibody that recognizes hyperacetylation of histone H4 (Upstate cat# 06-866) in the Western blotting assay or nuclear acetylation (Abcam cat# ab21623) in the immunofluorescence assay.

Example 19: In vivo Tumor Efficacy Model

[00219] Female NCr-Nude mice (age 6-8 weeks, Charles River Labs) are aseptically injected into the subcutaneous space in the right dorsal flank with 1.0-5.0 x 10^6 cells (SKOV-3, HCT-116, BxPC3) in 100 µL of a 1:1 ratio of serum-free culture media (Sigma Aldrich) and BD Matrigel™ (BD Biosciences) using a 1 mL 26 3/8 gauge needle (Becton Dickinson Ref#309625). Alternatively, some xenograft models

require the use of more immunocompromised strains of mice such as CB-17 SCID (Charles River Labs) or NOD-SCID (Jackson Laboratory). Furthermore, some xenograft models require serial passaging of tumor fragments in which small fragments of tumor tissue (approximately 1 mm^3) are implanted subcutaneously in the right dorsal flank of anesthetized (3-5% isoflourane/oxygen mixture) NCr-Nude, CB-17 SCID or NOD-SCID mice (age 5-8 weeks, Charles River Labs or Jackson Laboratory) via a 13-ga trocar needle (Popper & Sons 7927). Tumor volume is monitored twice weekly with Vernier calipers. The mean tumor volume is calculated using the formula $V = W^2 \times L /2$. When the mean tumor volume is approximately 200 mm^3, the animals are randomized into treatment groups of ten animals each. Drug treatment typically includes the test compound as a single agent, and may include combinations of the test compound and other anticancer agents. Dosing and schedules are determined for each experiment based on previous results obtained from pharmacokinetic/pharmacodynamic and maximum tolerated dose studies. The control group will receive vehicle without any drug. Typically, test compound (100-200 μL) is administered via intravenous (27-ga needle), oral (20-ga gavage needle) or subcutaneous (27-ga needle) routes at various doses and schedules. Tumor size and body weight are measured twice a week and the study is terminated when the control tumors reach approximately 2000 mm^3, and/or if tumor volume exceeds 10% of the animal body weight or if the body weight loss exceeds 20%.

[00220] The differences in tumor growth trends over time between pairs of treatment groups are assessed using linear mixed effects regression models. These models account for the fact that each animal is measured at multiple time points. A separate model is fit for each comparison, and the areas under the curve (AUC) for each treatment group are calculated using the predicted values from the model. The percent decrease in AUC (dAUC) relative to the reference group is then calculated. A statistically significant *P* value suggests that the trends over time for the two treatment groups are different.

[00221] The tumor measurements observed on a date pre-specified by the researcher (typically the last day of treatment) are analyzed to assess tumor growth inhibition. For this analysis, a T/C ratio is calculated for each animal by dividing the tumor measurement for the given animal by the mean tumor measurement across all control animals. The T/C ratios across a treatment group are compared to the T/C ratios of the control group using a two-tailed Welch's t-test. To adjust for multiplicity, a False Discovery Rate (FDR) is calculated for each comparison using the approach described by Benjamini and Hochberg, *J.R. Stat. Soc. B* **1995**, 57:289-300.

[00222] As detailed above, compounds of the invention inhibit HDAC6. In certain embodiments, compounds of the invention inhibit HDAC6 with the percent inhibition at a concentration of 1.235 μM shown in the table below.

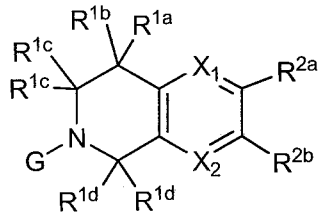
Compound	Percent Inhibition at 1.235 μM	Compound	Percent Inhibition at 1.235 μM
I-3	95.255	**I-9**	95.195
I-38	60.24	**I-4**	97.23
I-30	84.99	**I-37**	93.685
I-23	91.95	**I-48**	91.115
I-1	87.79	**I-41**	93.365
I-12	94.49	**I-15**	95.59
I-31	93.775	**I-10**	84.57
I-52	97.36	**I-21**	73.89
I-56	92.985	**I-28**	91.895
I-5	93.44	**I-16**	27.33
I-32	93	**I-47**	34.335
I-53	96.92	**I-36**	26.515
I-44	94.87	**I-55**	58.26
I-39	92.45	**I-54**	67.155
I-42	97.53	**I-8**	40.43
I-50	95.12	**I-34**	48.16
I-29	97.82	**I-13**	70.64
I-35	66.98	**I-17**	41.19
I-19	79.49	**I-51**	63.365
I-46	58.99	**I-25**	60.415
I-2	34.13	**I-40**	50.395
I-14	89.92	**I-43**	23.37
I-27	51.24	**I-45**	38.985
I-22	90.205	**I-20**	58.6
I-7	79.04	**I-59**	67.43
I-11	73.9	**I-58**	94.465
I-33	68.79	**I-61**	-3.95
I-49	94.1	**I-57**	94.12
I-6	81.38	**I-60**	75.78
I-24	92.33	**I-62**	94.65
I-18	97.215	**I-26**	93.995

[00223] As detailed above, compounds of the invention are selective for HDAC6 over other Class I HDAC enzymes. In some embodiments, the ratio of HDAC IC50 (as obtained in the nuclear extract assay described above) to HDAC6 IC50 is less than 5 (HDAC IC50/HDAC6 IC50). In certain embodiments, the ratio of HDAC IC50 to HDAC6 IC50 is between 5 and 10. In certain embodiments, the ratio of HDAC IC50 to HDAC6 IC50 is between 10 and 100.

[00224] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments, which utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments, which have been represented by way of examples.

WHAT IS CLAIMED IS:

1. A compound of formula (*I*):



(*I*);

or a pharmaceutically acceptable salt thereof;

wherein:

one of X_1 and X_2 is CR^1 and the other is N; or both X_1 and X_2 are N;

one of R^{2a} and R^{2b} is R^1, and the other is -C(O)-NH-OH;

R^{1a} is hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl;

R^{1b} is hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl;

or R^{1a} and R^{1b} are taken together to form a 3 to 6 membered cycloaliphatic;

R^{1c} and R^{1d} are:

I) each occurrence of R^{1c} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl; and each occurrence of R^{1d} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl; or

II) two occurrences of R^{1c} are taken together to form =O; and each occurrence of R^{1d} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl; or

III) two occurrences of R^{1d} are taken together to form =O; and each occurrence of R^{1c} is independently hydrogen, fluoro, C_{1-4} alkyl, or C_{1-4} fluoroalkyl;

each occurrence of R^1 is independently hydrogen, chloro, fluoro, -O-C_{1-4} alkyl, cyano, hydroxy, C_{1-4} alkyl, or C_{1-4} fluoroalkyl;

G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, $-L_2-V_1-R^3$, $-L_2-V_2-R^3$, $-V_1-L_1-V_2-R^3$, or $-L_1-R^3$;

L_1 is unsubstituted or substituted C_{1-3} alkylene chain;

L_2 is unsubstituted or substituted C_{2-3} alkylene chain;

V_1 is -C(O)-, -C(S)-, -C(O)-N(R^{4a})-, -C(O)-O-, -$S(O)_2$-, or -SO_2-N(R^{4a})-;

V_2 is -N(R^{4a})-, -N(R^{4a})-C(O)-, -N(R^{4a})-SO_2-, -SO_2-N(R^{4a})-, -SO_2-, -C(O)-, -C(O)-O-, -O-C(O)-, -O-, -S-, -N(R^{4a})-C(O)-N(R^{4a})-, -N(R^{4a})-C(O)-O-, -O-C(O)-N(R^{4a})-, or -N(R^{4a})-SO_2-N(R^{4a})-;

R^3 is unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each occurrence of R^{4a} is independently hydrogen, or unsubstituted or substituted C_{1-4} aliphatic.

2. The compound of claim 1, wherein:

R^{2a} is C(O)-NH-OH;

R^{2b} is R^1; and

X_1 is CR^1 and X_2 is N.

3. The compound of claim 1, wherein:

G is -R^3, -V_1-R^3, -V_1-L_1-R^3, or -L_1-R^3; and

V_1 is -C(O)-, -C(O)-N(R^{4a})-, or -$S(O)_2$-.

4. The compound of claim 1, wherein:

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl.

5. The compound of claim 1, wherein:

R^{1a} is hydrogen, fluoro, or methyl;

R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl; and

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl.

6. The compound of claim 1, wherein:

each substitutable carbon chain atom in R^3 is unsubstituted or substituted with 1-2 occurrences of $-R^{5dd}$;

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with =O, $=C(R^5)_2$, or $-R^{5aa}$;

each substitutable unsaturated ring carbon atom in R^3 is unsubstituted or is substituted with $-R^{5a}$;

each substitutable ring nitrogen atom in R^3 is unsubstituted or substituted with $-R^{9b}$;

each R^{5a} is independently halogen, $-NO_2$, -CN, $-C(R^5)=C(R^5)_2$, $-C\equiv C-R^5$, $-OR^5$, $-SR^6$, $-S(O)R^6$, $-SO_2R^6$, $-SO_2N(R^4)_2$, $-N(R^4)_2$, $-NR^4C(O)R^5$, $-NR^4C(O)N(R^4)_2$, $-NR^4CO_2R^6$, $-OC(O)N(R^4)_2$, $-C(O)R^6$, $-C(O)N(R^4)_2$, $-N(R^4)SO_2R^6$, $-N(R^4)SO_2N(R^4)_2$, unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two adjacent R^{5a}, taken together with the intervening ring atoms, form an unsubstituted or substituted fused 5-10 membered aromatic ring or an unsubstituted or substituted 4-10 membered non-aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each occurrence of R^{5aa} is independently chloro, fluoro, hydroxy, unsubstituted or substituted C_{1-6} aliphatic, $-O(C_{1-6}$ alkyl), $-C_{1-6}$ fluoroalkyl, $-O-C_{1-6}$ fluoroalkyl, cyano, $-N(R^4)_2$, $-C(O)(C_{1-6}$ alkyl), $-CO_2H$, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)N(C_{1-6}$ alkyl$)_2$, $-NHC(O)C_{1-6}$ alkyl, $-NHC(O)OC_{1-6}$ alkyl, $-NHC(O)NHC_{1-6}$ alkyl, or $-NHS(O)_2C_{1-6}$ alkyl;

each occurrence of R^{5dd} is independently fluoro, hydroxy, $-O(C_{1-6}$ alkyl), cyano, $-N(R^4)_2$, $-C(O)(C_{1-6}$ alkyl), $-CO_2H$, $-C(O)NH_2$, $-C(O)NH(C_{1-6}$ alkyl),

-C(O)N(C_{1-6} alkyl)$_2$, -NHC(O)C_{1-6} alkyl, -NHC(O)OC_{1-6} alkyl, -NHC(O)NHC_{1-6} alkyl, or -NHS(O)$_2C_{1-6}$ alkyl;

each R^4 is independently hydrogen, unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or two R^4 on the same nitrogen atom, taken together with the nitrogen atom, form an unsubstituted or substituted 5- to 6-membered heteroaryl or an unsubstituted or substituted 4- to 8-membered heterocyclyl having, in addition to the nitrogen atom, 0-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur;

each R^5 is independently hydrogen, unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

each R^6 is independently unsubstituted or substituted C_{1-6} aliphatic, unsubstituted or substituted 3-10-membered cycloaliphatic, unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^{9b} is independently -C(O)R^6, -C(O)N(R^4)$_2$, -CO_2R^6, -SO_2R^6, -SO_2N(R^4)$_2$, unsubstituted C_{3-10} cycloaliphatic, C_{3-10} cycloaliphatic substituted with 1-2 independent occurrences of R^7or R^8, unsubstituted C_{1-6} aliphatic, or C_{1-6} aliphatic substituted with 1-2 independent occurrences of R^7or R^8;

each R^7 is independently unsubstituted or substituted 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, unsubstituted or substituted 6-10-membered aryl, or unsubstituted or substituted 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^8 is independently chloro, fluoro, -OH, -O(C_{1-6} alkyl), -CN, -N(R^4)$_2$,

-C(O)(C_{1-6} alkyl), -CO_2H, -CO_2(C_{1-6} alkyl), -C(O)NH_2, -C(O)NH(C_{1-6} alkyl), or -C(O)N(C_{1-6} alkyl)$_2$.

7. The compound of claim 6, wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5aa}$;

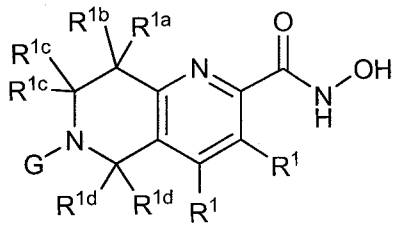
the total number of R^{5a} and R^{5aa} substituents is p;

p is 1-4;

each R^{5a} is independently halogen, cyano, nitro, hydroxy, unsubstituted C_{1-6} aliphatic, C_{1-6} aliphatic substituted with 1-2 independent occurrences of R^7or R^8, unsubstituted –O-C_{1-6} alkyl, -O-C_{1-6} alkyl substituted with 1-2 independent occurrences of R^7or R^8, C_{1-6} fluoroalkyl, -O-C_{1-6} fluoroalkyl, -NHC(O)R^6, -C(O)NH(R^4), -NHC(O)O-C_{1-6} alkyl, -NHC(O)NHC_{1-6} alkyl, -NHS(O)$_2C_{1-6}$ alkyl, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, 3-10-membered cycloaliphatic substituted with 0-2 occurrences of $-R^{7a}$, 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with 0-2 occurrences of $-R^{7a}$, 6-10-membered aryl substituted with 0-2 occurrences of $-R^{7a}$, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with 0-2 occurrences of $-R^{7a}$, and

each occurrence of R^{7a} is independently chloro, fluoro, C_{1-6} aliphatic, C_{1-6} fluoroalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} fluoroalkyl, cyano, hydroxy, -CO_2H, -NHC(O)C_{1-6} alkyl, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -C(O)NHC_{1-6} alkyl, -C(O)N(C_{1-6} alkyl)$_2$, -NHC(O)NHC_{1-6} alkyl, -NHC(O)N(C_{1-6} alkyl)$_2$, or -NHS(O)$_2C_{1-6}$ alkyl.

8. The compound of claim 6, represented by formula (***II-a-i***):



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(*II-a-i*).

9. The compound of claim 8, wherein:

G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, or $-L_1-R^3$; and

V_1 is -C(O)-, $-C(O)-N(R^{4a})-$, or $-S(O)_2-$.

10. The compound of claim 9, wherein:

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl.

11. The compound of claim 9, wherein:

R^{1a} is hydrogen, fluoro, or methyl;

R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl; and

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl.

12. The compound of claim 9, wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5aa}$;

the total number of R^{5a} and R^{5aa} substituents is p;

p is 1-4;

each R^{5a} is independently halogen, cyano, nitro, hydroxy, unsubstituted C_{1-6} aliphatic, C_{1-6} aliphatic substituted with 1-2 independent occurrences of R^7or R^8, unsubstituted –O-C_{1-6} alkyl, -O-C_{1-6} alkyl substituted with 1-2 independent occurrences of R^7or R^8, C_{1-6} fluoroalkyl, -O-C_{1-6} fluoroalkyl, -NHC(O)R^6, -C(O)NH(R^4), -NHC(O)O-C_{1-6} alkyl, -NHC(O)NHC_{1-6} alkyl, -NHS(O)$_2$$C_{1-6}$ alkyl, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, 3-10-membered cycloaliphatic substituted with 0-2 occurrences of –R^{7a}, 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with 0-2 occurrences of –R^{7a}, 6-10-membered aryl substituted with 0-2 occurrences of –R^{7a}, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with 0-2 occurrences of –R^{7a}, and

each occurrence of R^{7a} is independently chloro, fluoro, C_{1-6} aliphatic, C_{1-6} fluoroalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} fluoroalkyl, cyano, hydroxy, -CO_2H, -NHC(O)C_{1-6} alkyl, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -C(O)NHC_{1-6} alkyl, -C(O)N(C_{1-6} alkyl)$_2$, -NHC(O)NHC_{1-6} alkyl, -NHC(O)N(C_{1-6} alkyl)$_2$, or -NHS(O)$_2$$C_{1-6}$ alkyl.

13. The compound of claim 12, wherein:

R^{1a} is hydrogen;

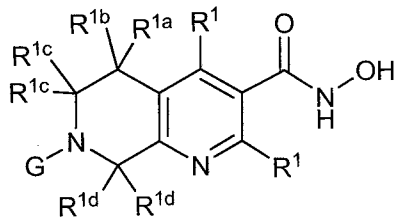
R^{1b} is hydrogen;

each occurrence of R^{1c} is hydrogen;

each occurrence of R^{1d} is hydrogen; and

each occurrence of R^1 is hydrogen.

14. The compound of claim 6, represented by formula (***II-a-ii***):



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(***II-a-ii***).

15. The compound of claim 14, wherein:

G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, or $-L_1-R^3$; and

V_1 is $-C(O)-$, $-C(O)-N(R^{4a})-$, or $-S(O)_2-$.

16. The compound of claim 15, wherein:

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl.

17. The compound of claim 15, wherein:

R^{1a} is hydrogen, fluoro, or methyl;

R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl; and

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl.

18. The compound of claim 15, wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5aa}$;

the total number of R^{5a} and R^{5aa} substituents is p;

p is 1-4;

each R^{5a} is independently halogen, cyano, nitro, hydroxy, unsubstituted C_{1-6} aliphatic, C_{1-6} aliphatic substituted with 1-2 independent occurrences of R^7or R^8, unsubstituted $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl substituted with 1-2 independent occurrences of R^7or R^8, C_{1-6} fluoroalkyl, $-O-C_{1-6}$ fluoroalkyl, $-NHC(O)R^6$, $-C(O)NH(R^4)$, $-NHC(O)O-C_{1-6}$ alkyl, $-NHC(O)NHC_{1-6}$ alkyl, $-NHS(O)_2C_{1-6}$ alkyl, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, 3-10-membered cycloaliphatic substituted with 0-2 occurrences of $-R^{7a}$, 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with 0-2 occurrences of $-R^{7a}$, 6-10-membered aryl substituted with 0-2 occurrences of $-R^{7a}$, or 5-10-

membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with 0-2 occurrences of $-R^{7a}$, and

each occurrence of R^{7a} is independently chloro, fluoro, C_{1-6} aliphatic, C_{1-6} fluoroalkyl, -O-C_{1-6} alkyl, -O-C_{1-6} fluoroalkyl, cyano, hydroxy, $-CO_2H$, -NHC(O)C_{1-6} alkyl, -NHC_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -C(O)NHC_{1-6} alkyl, -C(O)N(C_{1-6} alkyl)$_2$, -NHC(O)NHC_{1-6} alkyl, -NHC(O)N(C_{1-6} alkyl)$_2$, or -NHS(O)$_2$$C_{1-6}$ alkyl.

19. The compound of claim 18, wherein:

R^{1a} is hydrogen;

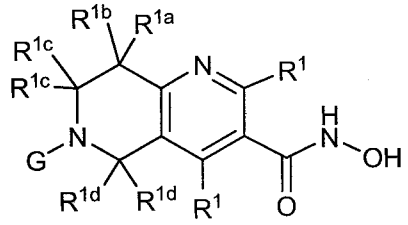
R^{1b} is hydrogen;

each occurrence of R^{1c} is hydrogen;

each occurrence of R^{1d} is hydrogen; and

each occurrence of R^1 is hydrogen.

20. The compound of claim 6, represented by formula (***II-b-i***):



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(***II-b-i***).

21. The compound of claim 20, wherein:

G is $-R^3$, $-V_1-R^3$, $-V_1-L_1-R^3$, or $-L_1-R^3$; and

V_1 is -C(O)-, -C(O)-N(R^{4a})-, or $-S(O)_2-$.

22. The compound of claim 21, wherein:

each occurrence of R^1 is independently hydrogen, chloro, fluoro, cyano, hydroxy, methoxy, ethoxy, trifluoromethyl, methyl, or ethyl.

23. The compound of claim 21, wherein:

R^{1a} is hydrogen, fluoro, or methyl;

R^{1b} is hydrogen, fluoro, or methyl;

each occurrence of R^{1c} is independently hydrogen, fluoro, or methyl; and

each occurrence of R^{1d} is independently hydrogen, fluoro, or methyl.

24. The compound of claim 21, wherein:

each substitutable saturated ring carbon atom in R^3 is unsubstituted or substituted with $-R^{5aa}$;

the total number of R^{5a} and R^{5aa} substituents is p;

p is 1-4;

each R^{5a} is independently halogen, cyano, nitro, hydroxy, unsubstituted C_{1-6} aliphatic, C_{1-6} aliphatic substituted with 1-2 independent occurrences of R^7or R^8, unsubstituted $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl substituted with 1-2 independent occurrences of R^7or R^8, C_{1-6} fluoroalkyl, $-O-C_{1-6}$ fluoroalkyl, $-NHC(O)R^6$, $-C(O)NH(R^4)$, $-NHC(O)O-C_{1-6}$ alkyl, $-NHC(O)NHC_{1-6}$ alkyl, $-NHS(O)_2C_{1-6}$ alkyl, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, 3-10-membered cycloaliphatic substituted with 0-2 occurrences of $-R^{7a}$, 4-10-membered heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with 0-2 occurrences of $-R^{7a}$, 6-10-membered aryl substituted with 0-2 occurrences of $-R^{7a}$, or 5-10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with 0-2 occurrences of $-R^{7a}$, and

each occurrence of R^{7a} is independently chloro, fluoro, C_{1-6} aliphatic, C_{1-6} fluoroalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ fluoroalkyl, cyano, hydroxy, $-CO_2H$, $-NHC(O)C_{1-6}$ alkyl, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-C(O)NHC_{1-6}$ alkyl, $-C(O)N(C_{1-6}$ alkyl$)_2$, $-NHC(O)NHC_{1-6}$ alkyl, $-NHC(O)N(C_{1-6}$ alkyl$)_2$, or $-NHS(O)_2C_{1-6}$ alkyl.

25. The compound of claim 24, wherein:

R^{1a} is hydrogen;

R^{1b} is hydrogen;

each occurrence of R^{1c} is hydrogen;

each occurrence of R^{1d} is hydrogen; and

each occurrence of R^{1} is hydrogen.

26. A pharmaceutical composition comprising a compound of any of claims 1-25, and a pharmaceutically acceptable carrier.

27. A method of treating a proliferative disorder in a patient comprising administering to said patient a therapeutically effective amount of a compound of any of claims 1-25.

28. The method of claim 27, wherein the proliferative disorder is breast cancer, lung cancer, ovarian cancer, multiple myeloma, acute myeloid leukemia, or acute lymphoblastic leukemia.

29. A compound or a pharmaceutically acceptable salt of any of claims 1-25 or a pharmaceutical composition thereof for use in treating a proliferative disorder in a patient in need thereof.

30. The compound or pharmaceutically acceptable salt or pharmaceutical composition thereof according to claim 29, wherein the proliferative disorder is breast cancer, lung cancer, ovarian cancer, multiple myeloma, acute myeloid leukemia, or acute lymphoblastic leukemia.

31. A pharmaceutical composition for the treatment of a proliferative disorder in a patient in need thereof comprising a compound or a pharmaceutically acceptable salt of any of claims 1-25 as the active ingredient, and a pharmaceutically acceptable carrier.

32. The pharmaceutical composition according to claim 31, wherein the proliferative disorder is breast cancer, lung cancer, ovarian cancer, multiple myeloma, acute myeloid leukemia, or acute lymphoblastic leukemia.

33. Use of a compound or a pharmaceutically acceptable salt of any of claims 1-25 for the preparation of a pharmaceutical composition for the treatment of a proliferative disorder.

34. The use according to claim 33, wherein the proliferative disorder is breast cancer, lung cancer, ovarian cancer, multiple myeloma, acute myeloid leukemia, or acute lymphoblastic leukemia.

35. Use of an effective amount of a compound or a pharmaceutically acceptable salt of any of claims 1-25 or a pharmaceutical composition thereof for the treatment of a proliferative disorder in a patient in need thereof.

36. The use according to claim 35, wherein the proliferative disorder is breast cancer, lung cancer, ovarian cancer, multiple myeloma, acute myeloid leukemia, or acute lymphoblastic leukemia.

37. Use of a compound or a pharmaceutically acceptable salt according to any of claims 1-25 in the manufacture of a medicament for treating a proliferative disorder.

38. The use according to claim 37, wherein the proliferative disorder is breast cancer, lung cancer, ovarian cancer, multiple myeloma, acute myeloid leukemia, or acute lymphoblastic leukemia.

39. A method for inhibiting HDAC6 activity in a patient comprising administering a pharmaceutical composition comprising an amount of a compound of any of claims 1-25 effective to inhibit HDAC6 activity in the patient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/49136

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/28; A61K 31/215 (2011.01)
USPC - 514/507
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/507

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/575 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PUBWEST (PGPB,USPT,EPAB,JPAB), Google Scholar
histone deacetylase, HDAC, inhibit$, modulat$, hydroxamic acid, hydroxamide, pyridopyridine, $tetrahydropyrido$pyridine, $tetrahydropyrido$pyrazine, cancer, tumor, carcinoma, neoplas$, lung, breast, ovar$, leukemia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0004041 A1 (CUMMINGS et al.) 05 January 2006 (05.01.2006) para [0012]-[0029], [0094]	1-39
Y	US 2005/0148613 A1 (VAN EMELEN et al.) 07 July 2005 (07.07.2005) para [0001], [0123]-[0125], [0142], [0147], [0258], [0268]-[0269], [0291], Table F-2.	1-39
Y	WO 2009/129335 A2 (VERNER et al.) 22 October 2009 (22.10.2009) para [0002]; pg 64, Table 4	8-13
A	US 7,250,514 B1 (XIAO) 31 July 2007 (31.07.2007) col 3, ln 40 to col 44, ln 37	1-39

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 December 2011 (30.12.2011)	20 JAN 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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