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(54) Title: CINNAMIC ACID HYDROXYAMIDES AS INHIBITORS OF HISTONE DEACETYLASE 8

(57) Abstract: Described herein are compounds and pharmaceutical compositions containing such compounds, which inhibit the activy of histone deacetylase 8 (HDAC8). Also described herein are methods of using such HDAC8 inhibitors, alone and in combination with other compounds, for treating diseases or conditions that would benefit from inhibition of HDAC8 activity.

CINNAMIC ACID HYDROXYAMIDES AS INHIBITORS OF HISTONE DEACETYLASE 8

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S provisional patent application no. 61/581,459 entitled "CINNAMIC ACID HYDROXYAMIDES AS INHIBITORS OF HISTONE DEACETYLASE 8" filed on December 29, 2011, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments that include such compounds, and methods of using such compounds to inhibit the activity of histone deacetylase 8.

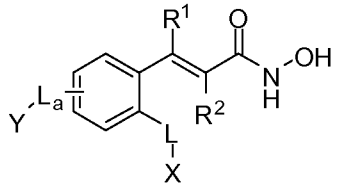
BACKGROUND OF THE INVENTION

[0003] Histone deacetylases (HDACs) catalyze the removal of acetyl groups from histones, proteins that organize and modulate the structure of chromatin in nucleosomes. HDAC-mediated deacetylation of chromatin-bound histones regulates the expression of a variety of genes throughout the genome. Importantly, HDACs have been linked to cancer, as well as other health conditions. To date, eleven major HDAC isoforms have been described (HDACs 1-11). HDACs are categorized into two classes. Class I HDACs include HDAC1, HDAC2, HDAC3, HDAC8 and HDAC11. Class II HDACs include HDAC4, HDAC5, HDAC6, HDAC7, HDAC9 and HDAC10. Small molecule HDAC inhibitors that are isoform-selective are useful as therapeutic agents with reduced toxicity and as tools for probing the biology of the HDAC isoforms.

SUMMARY OF THE INVENTION

[0004] In one aspect provided herein are substituted cinnamic acid hydroxyamide compounds and other HDAC8 inhibitors, pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof. In some embodiments, the compounds described herein inhibit HDAC8 activity. In some embodiments, the compounds described herein are used to treat mammals where inhibition of HDAC8 activity provides benefit. Compounds described herein are HDAC8 inhibitors.

[0005] In one aspect, described herein is a compound having a structure of Formula (I):



Formula (I);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

L and L_a are each independently a bond, O, S, NR^3, -$NR^{10}C(=O)$-R^{11}, S(=O), $S(=O)_2$, $NHS(=O)_2$, -C_1-C_6alkylene-, -C_2-C_6alkenylene-, -C_2-C_6alkynylene-, -C_1-C_6heteroalkylene-, -C_1-C_6alkylene-O-, -C_1-C_3alkylene-O-C_1-C_3alkylene-, -C_1-C_6alkylene-NR^3-, -C_1-C_3alkylene-NR^3-C_1-C_3alkylene -, -C_1-C_6alkylene-$C(=O)NR^3$-, -C_1-C_3alkylene-$C(=O)NR^3$-C_1-C_3alkylene -, -C_1-C_6alkylene-$NR^3C(=O)$-, -C_1-C_3alkylene-$NR^3C(=O)$-C_1-C_3alkylene-, -C_1-C_6alkylene-S-, -C_1-C_3alkylene-S-C_1-C_3alkylene-, -C_1-C_6alkylene-S(=O)-, -C_1-C_3alkylene-S(=O)-C_1-C_3alkylene, -C_1-C_6alkylene-$S(=O)_2$-, -C_1-C_3alkylene-$S(=O)_2$-C_1-C_3alkylene,–C(=O)-, or –C(=O)-C_1-C_6alkylene;

X is a substituted or unsubstituted group selected from among aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if X is substituted, then X is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -$C(=O)R^{11}$, -S-R^{11}, -$S(=O)$-R^{11}, -$S(=O)_2$-R^{11}, -$NR^{10}C(=O)$-R^{11}, -$C(=O)N(R^{10})_2$, -$S(=O)_2N(R^{10})_2$, -$NR^{10}S(=O)_2$-R^{11}, -$OC(=O)N(R^{10})_2$, -$NR^{10}C(=O)O$-R^{11}, -$OC(=O)O$-R^{11}, -$NHC(=O)NH$-R^{11}, -$OC(=O)$-R^{11}, -$N(R^{10})_2$, -C_1-C_2alkyl$N(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

Y is H or a substituted or unsubstituted group selected from among C_1-C_6alkyl, -CO_2R^{10}, -$C(=O)R^{11}$, -$NR^{10}C(=O)$-R^{11}, -$C(=O)N(R^{10})_2$, aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if Y is substituted, then Y is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -

CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -S(=O)$_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -S(=O)$_2$N(R^{10})$_2$, -NR^{10}S(=O)$_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^3 is H, C_1-C_6alkyl, phenyl or benzyl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[0006] For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments, R^1 is hydrogen or C_1-C_6alkyl. In some other embodiments, R^2 is hydrogen or C_1-C_6alkyl. In other embodiments, R^1 and R^2 are each hydrogen.

[0007] In one embodiment, L is O or S.

[0008] In another embodiment, X is a substituted or unsubstituted aryl. In yet another embodiment, aryl is phenyl.

[0009] In a further embodiment, phenyl is substituted with at least one Cl, Br, I, or F. In yet a further embodiment, phenyl is substituted with at least two of Cl, Br, I, or F.

[0010] In one embodiment, phenyl is substituted with at least one C_1-C_6alkyl. In another embodiment, C_1-C_6alkyl is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl.

[0011] In yet another embodiment, C_1-C_6alkyl is methyl.

[0012] In a further embodiment, phenyl is substituted with at least one C_1-C_6alkoxy. In yet a further embodiment, C_1-C_6alkoxy is selected from methoxy or ethoxy.

[0013] In one embodiment, X is a substituted or unsubstituted heteroaryl. In another embodiment, heteroaryl is pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, 4-azaindolyl, 5-azaindolyl, 6-azaindolyl, 7-azaindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl,

benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl.

[0014] In yet another embodiment, heteroaryl is pyridinyl.

[0015] In a further embodiment, X is a substituted or unsubstituted C_3-C_{10}cycloalkyl. In yet a further embodiment, C_3-C_{10}cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0016] In one embodiment, X is a substituted or unsubstituted C_2-C_{10}heterocycloalkyl.

[0017] In another embodiment, C_2-C_{10}heterocycloalkyl is quinolizinyl, dioxinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiazinyl, tetrahydropyridinyl, piperazinyl, oxazinanonyl, dihydropyrrolyl, dihydroimidazolyl, tetrahydrofuranyl, tetrahydropyranyl, dihydrooxazolyl, oxiranyl, pyrrolidinyl, pyrazolidinyl, dihydrothienyl, imidazolidinonyl, pyrrolidinonyl, dihydrofuranonyl, dioxolanonyl, thiazolidinyl, piperidinonyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and tetrahydrothienyl. In yet another embodiment, C_2-C_{10}heterocycloalkyl is piperidinyl. In a further embodiment, piperidinyl is substituted with -CO_2R^{10}, -C(=O)R^{11} or -C(=O)N(R^{10})$_2$. In yet a further embodiment, piperidinyl is substituted with –C(=O)R^{11}.

[0018] In one embodiment, R^{11} is a substituted or unsubstituted C_1-C_6alkyl. In another embodiment, C_1-C_6alkyl is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl.

[0019] In yet another embodiment, C_1-C_6alkyl is methyl or iso-propyl.

[0020] In a further embodiment, R^{11} is a substituted or unsubstituted aryl. In yet a further embodiment, aryl is a phenyl group.

[0021] In one embodiment, R^{11} is a substituted or unsubstituted heteroaryl. In another embodiment, heteroaryl is pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, 4-azaindolyl, 5-azaindolyl, 6-azaindolyl, 7-azaindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl. In yet another embodiment, heteroaryl is pyridinyl or furanyl.

[0022] In one aspect is a compound selected from (E)-N-hydroxy-3-(2-(3-methoxyphenoxy)phenyl)acrylamide; (E)-3-(2-(3-fluorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-N-hydroxy-3-(2-(pyridin-3-yloxy)phenyl)acrylamide; (E)-N-hydroxy-3-(2-(pyridin-4-yloxy)phenyl)acrylamide; (E)-N-hydroxy-3-(2-(4-methoxyphenoxy)phenyl)acrylamide; (E)-3-(2-(3-chlorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)phenyl)-N-

hydroxyacrylamide; (E)-N-hydroxy-3-(2-(m-tolyloxy)phenyl)acrylamide; (E)-N-hydroxy-3-(2-phenoxyphenyl)acrylamide; (E)-N-hydroxy-3-(2-(p-tolyloxy)phenyl)acrylamide; (E)-3-(2-(4-chlorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)phenyl)-N-hydroxyacrylamide; (S,E)-3-(2-(1-benzoylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (S,E)-3-(2-(1-acetylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (S,E)-N-hydroxy-3-(2-(1-isobutyrylpiperidin-3-yloxy)phenyl)acrylamide; (E)-3-(2-(1-(furan-2-carbonyl)piperidin-4-yloxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(1-acetylpiperidin-4-yloxy)phenyl)-N-hydroxyacrylamide; (E)-N-hydroxy-3-(2-(1-isobutyrylpiperidin-4-yloxy)phenyl)acrylamide; (E)-3-(2-(1-benzoylpiperidin-4-yloxy)phenyl)-N-hydroxyacrylamide; (E)-N-hydroxy-3-(2-(1-nicotinoylpiperidin-4-yloxy)phenyl)acrylamide; (R,E)-3-(2-(1-acetylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (S,E)-3-(2-(1-(furan-2-carbonyl)piperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (R,E)-3-(2-(1-(furan-2-carbonyl)piperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (R,E)-N-hydroxy-3-(2-(1-isobutyrylpiperidin-3-yloxy)phenyl)acrylamide; (R,E)-3-(2-(1-benzoylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (R,E)-N-hydroxy-3-(2-(1-nicotinoylpiperidin-3-yloxy)phenyl)acrylamide; (S,E)-N-hydroxy-3-(2-(1-nicotinoylpiperidin-3-yloxy)phenyl)acrylamide; (E)-N-(4-(4-fluorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide; (E)-3-(5-acetamido-2-(4-fluorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(5-acetamido-2-(3-chlorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-N-(4-(3-chlorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide; (E)-N-(4-(3-fluorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide; (E)-N-(4-(3,4-dichlorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide; (E)-3-(5-acetamido-2-(3-fluorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-5-(methylsulfonamido)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-5-(methylsulfonamido)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-fluorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-fluorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-4-(pyridin-3-ylmethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-4-(2-morpholinoethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-4-(2-(4-

methylpiperazin-1-yl)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-4-(2-(dimethylamino)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-4-(2-methoxyethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-fluorophenoxy)-4-(2-methoxyethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(4-(2-acetamidoethoxy)-2-(3-chlorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-fluorophenoxy)-4-(2-(dimethylamino)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-fluorophenoxy)-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-4-(2-methoxyethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-4-(pyridin-3-ylmethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-4-(2-(dimethylamino)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(4-(2-acetamidoethoxy)-2-(4-fluorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)-4-(2-methoxyethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(4-(2-acetamidoethoxy)-2-(3,4-dichlorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)-4-(2-morpholinoethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)-4-(pyridin-3-ylmethoxy)phenyl)-N-hydroxyacrylamide; an active metabolite, pharmaceutically acceptable solvate, pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[0023] Further disclosed herein are pharmaceutical compositions comprising a compound of Formula (I), (II), (III), (IIIa), (IV), (IVa), (IVb), or (IVc) or an active metabolite, pharmaceutically acceptable solvate, pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof and a pharmaceutically acceptable diluent, excipient, or carrier. In some embodiments, the pharmaceutical compositions are formulated for intravenous injection, subcutaneous injection, oral administration, inhalation, nasal administration, topical administration, ophthalmic administration or otic administration. In some embodiments, the pharmaceutical compositions are formulated as a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye drop or an ear drop.

[0024] Additionally disclosed herein are pharmaceutical compositions comprising a HDAC8 inhibitor compound described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof and a pharmaceutically acceptable diluent, excipient, or carrier. In some emvodiments, the pharmaceutical compositions are formulated for intravenous injection, subcutaneous injection, oral administration, inhalation,

nasal administration, topical administration, ophthalmic administration or otic administration. In some embodiments, the pharmaceutical compositions are formulated as a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye drop or an ear drop.

[0025] Disclosed herein, in certain embodimens, are methods of treating T-cell lymphoma or leukemia in a mammal comprising administering a HDAC8 8 inhibitor compound described herein. In one aspect, the mammal is a human. In some embodiments, compounds described herein are orally administered.

[0026] In one aspect is the use of a HDAC8 8 inhibitor compound described herein for treating T-cell lymphoma or leukemia in a mammal. In one aspect, the mammal is a human. In some embodiments, compounds described herein are orally administered.

[0027] In one aspect is the use of a HDAC8 8 inhibitor compound described herein in the manufacture of a medicament for treating T-cell lymphoma or leukemia in a mammal. In one aspect, the mammal is a human. In some embodiments, compounds described herein are orally administered.

[0028] Also described herein are methods of treating a disease or condition mediated by interleukin-1 beta (IL-1b) or IL-18 in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a HDAC8 8 inhibitor compound described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof. In one aspect, the disease or condition is selected from among osteoarthritis, rheumatoid arthritis, septic arthritis, gout, pseudogout, juvenile arthritis, Still's disease, Ankylosing spondylitis, systemic lupus erythematosus (SLE), Henoch-Schönlein purpura, psoriatic arthritis, reactive arthritis (Reiter's syndrome), hemochromatosis, hepatitis, Wegener's granulomatosis, Familial Mediterranean fever (FMF), HIDS (hyperimmunoglobulinemia D and periodic fever syndrome), TRAPS (TNF-alpha receptor associated periodic fever syndrome), inflammatory bowel disease, Crohn's Disease, ulcerative colitis, recurrent fever, anemia, leukocytosis, asthma, chronic obstructive pulmonary disease, and myalgia. In one aspect, the method further comprises administering to the mammal a second therapeutic agent, selected from among tacrolimus, cyclosporin, rapamicin, methotrexate , cyclophosphamide, azathioprine, mercaptopurine, mycophenolate, or FTY720, prednisone, cortisone acetate, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, fludrocortisone acetate, deoxycorticosterone acetate, aldosterone, aspirin, salicylic acid, gentisic acid, choline magnesium

salicylate, choline salicylate, choline magnesium salicylate, choline salicylate, magnesium salicylate, sodium salicylate, diflunisal, carprofen, fenoprofen, fenoprofen calcium, flurobiprofen, ibuprofen, ketoprofen, nabutone, ketolorac, ketorolac tromethamine, naproxen, oxaprozin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, meclofenamate, meclofenamate sodium, mefenamic acid, piroxicam, meloxicam, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib, CS-502, JTE-522, L-745,337 and NS398, leflunomide, gold thioglucose, gold thiomalate, aurofin, sulfasalazine, hydroxychloroquinine, minocycline, infliximab, etanercept, adalimumab, abatacept, anakinra, interferon-β, interferon-γ, interleukin-2, allergy vaccines, antihistamines, antileukotrienes, beta-agonists, theophylline, and anticholinergics. In one aspect, the mammal is a human. In some embodiments, compounds described herein are orally administered.

[0029] In one aspect, HDAC8 8 inhibitor compounds described herein are for use in treating a disease or condition mediated by interleukin-1 beta (IL-1b) or IL-18 in a mammal. In one aspect, the disease or condition is selected from among osteoarthritis, rheumatoid arthritis, septic arthritis, gout, pseudogout, juvenile arthritis, Still's disease, Ankylosing spondylitis, systemic lupus erythematosus (SLE), Henoch-Schönlein purpura, psoriatic arthritis, reactive arthritis (Reiter's syndrome), hemochromatosis, hepatitis, Wegener's granulomatosis, Familial Mediterranean fever (FMF), HIDS (hyperimmunoglobulinemia D and periodic fever syndrome), TRAPS (TNF-alpha receptor associated periodic fever syndrome), inflammatory bowel disease, Crohn's Disease, ulcerative colitis, recurrent fever, anemia, leukocytosis, asthma, chronic obstructive pulmonary disease, and myalgia. In a further aspect, the HDAC8 8 inhibitor compounds described herein are used in combination with a second therapeutic agent, selected from among tacrolimus, cyclosporin, rapamicin, methotrexate , cyclophosphamide, azathioprine, mercaptopurine, mycophenolate, or FTY720, prednisone, cortisone acetate, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, fludrocortisone acetate, deoxycorticosterone acetate, aldosterone, aspirin, salicylic acid, gentisic acid, choline magnesium salicylate, choline salicylate, choline magnesium salicylate, choline salicylate, magnesium salicylate, sodium salicylate, diflunisal, carprofen, fenoprofen, fenoprofen calcium, flurobiprofen, ibuprofen, ketoprofen, nabutone, ketolorac, ketorolac tromethamine, naproxen, oxaprozin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, meclofenamate, meclofenamate sodium, mefenamic acid, piroxicam, meloxicam, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib, CS-502, JTE-522, L-745,337 and NS398, leflunomide, gold thioglucose, gold thiomalate, aurofin, sulfasalazine, hydroxychloroquinine, minocycline, infliximab, etanercept, adalimumab, abatacept, anakinra, interferon-β, interferon-γ,

interleukin-2, allergy vaccines, antihistamines, antileukotrienes, beta-agonists, theophylline, and anticholinergics. In one aspect, the mammal is a human. In some embodiments, compounds described herein are orally administered.

[0030] In one aspect is the use of a HDAC8 8 inhibitor compounds described herein in the manufacture of a medicament for treating a disease or condition mediated by interleukin-1 beta (IL-1b) or IL-18 in a mammal. In one aspect, the mammal is a human. In some embodiments, compounds described herein are orally administered.

[0031] In any of the aforementioned embodiments involving the treatment with a HDAC8 inhibitor compound are further embodiments comprising administering at least one additional agent in addition to the administration of a HDAC8 inhibitor compound. Each agent is administered in any order, including simultaneously.

[0032] In some embodiments, compounds described herein are used for inhibiting the activity of HDAC8 or for the treatment of a disease or condition that would benefit from inhibition of the activity of HDAC8.

[0033] In some embodiments, compounds described herein are used for the formulation of a medicament for the inhibition of HDAC8 activity.

[0034] Articles of manufacture, which include packaging material, a HDAC8 inhibitor compound described herein, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, prodrug, or pharmaceutically acceptable solvate thereof, is used for inhibiting the activity of HDAC8, or for the treatment, prevention or amelioration of one or more symptoms of a disease or condition that would benefit from inhibition of the activity of HDAC8, are provided.

[0035] Other objects, features and advantages of the methods, compounds, and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent from this detailed description.

DETAILED DESCRIPTION

[0036] Covalent modification of histone proteins through acetylation and deacetylation is an important determinant of chromatin structure and a regulator of gene expression. Acetylation of histone proteins occurs on lysine residues near the N-termini of these proteins. In conjunction with other modifications of histone proteins and DNA, the acetylation state of histones determines whether the chromatin is in a condensed, transcriptionally silent state or in a form

more accessible to the transcription machinery of the cell. In general, hyperacetylation of histone proteins is associated with transcriptional activation of genes. The steady-state histone acetylation level arises from the opposing action of histone acetyltransferase (HAT) and histone deacetylase (HDAC) enzymes.

[0037] Histone deacetylases (HDACs) catalyze the removal of acetyl groups from lysine ε–amino groups near the N-termini of histones. This reaction promotes the condensation of chromatin, leading to repression of transcription.

[0038] HDAC inhibitors (HDIs) modify gene expression positively or negatively in a cell- and gene-specific manner. HDIs increase the accumulation of acetylated histones, directly influencing chromatin structure and, thereby, the relationship of the nucleosome to gene promoter elements.

[0039] Histone deacetylase (HDAC) enzymes modulate gene expression through the deacetylation of acetylated lysine residues on histone proteins. They operate in biological systems as part of multiprotein corepressor complexes. Histone deacetylases have been grouped into three classes. Class I and class II histone deacetylases (HDACs) are zinc containing hydrolase enzymes. The division of the proteins into classes I and II is based on protein size, sequence similarity, and organization of the protein domains.

[0040] Members of class I are related to the yeast RPD3 gene product. Class I HDACs include: HDAC1; HDAC2; HDAC3; HDAC8; HDAC11.

[0041] HDAC8 is a 377 residue, 42 kDa protein localized to the nucleus of a wide array of tissues, as well as several human tumor cell lines. The wild-type form of full length HDAC8 is described in GenBank Accession Number NP 060956; Buggy, J. J. *et al.*, *Biochem. J.*, 350 (Pt 1), 199-205 (2000). The HDAC8 structure was solved with four different hydroxamate inhibitors bound (Somoza *et al.*, *Structure*, 2004, 12, 1325).

[0042] Class II are homologues of the yeast HDA1 protein, and include: HDAC4; HDAC5; HDAC6; HDAC7; HDAC9; HDAC10.

[0043] Class II HDACs have been further subdivided into classes IIa (HDACs 4, 5, 7, and 9) and IIb (HDACs 6 and 10).

[0044] The third class of deacetylases consists of the members of the Sir2 family of enzymes. These enzymes have histone deacetylase activity but are structurally and evolutionarily unrelated to the class I and class II proteins. They are (nicotinamide adenine dinucleotide) NAD-dependent and unlike class I HDACs and class II HDACs, they do not contain a catalytic zinc site.

[0045] In the cell, HDAC proteins are recruited as part of multicomponent repressor complexes. Several HDAC containing complexes have been characterized, including the N-

CoR/SMRT, Sin3, NuRD, and CoREST complexes. Within these complexes, HDACs 1 and 2 typically interact with the mSin3, Mi-2, or CoREST proteins. HDAC3 and the class IIa HDACs have been shown to interact with SMRT and the related N-CoR protein. A large number of transcription factors have been shown to bind to one of the corepressor complexes as a means of regulating transcription. The recruitment of HDACs by DNA-binding proteins allows histone deacetylation to be directed toward specific regions of the chromatin in order to promote targeted transcriptional repression.

[0046] HDAC proteins are promising therapeutic targets on account of their involvement in regulating genes involved in cell cycle progression and control. Inhibition of HDACs has been shown to upregulate genes, including p21WAF/CIP1, p27, p53, and cyclin E, and to downregulate genes such as cyclin A and cyclin D. Growth inhibition in several lines of cancer cells has been observed upon treatment with HDAC inhibitors, and *in vivo* studies have shown that some of these inhibitors are efficacious in slowing tumor growth. The biological activity of each of the HDAC isozymes is determined by a combination of the intrinsic activity of the enzyme and the effects of cofactor binding on reactivity and substrate recognition (Schultz *et al.*, *Biochemistry*, 2004, 43, 11083-11091).

[0047] Non-selective HDAC inhibitors inhibit the deacetylase activity of most, if not all, of the HDACs with equal potency. The mechanisms of the anticancer effects of SAHA, a non-selective HDAC inhibitor, are not completely understood, and likely result from both altered gene expression and altered function of proteins regulating cell proliferation and cell death pathways. Non-selective HDAC inhibitors, such as SAHA, induce the accumulation of acetylated histone proteins and non histone proteins. Non-histone proteins that are acetylated include, but are not limited to:

[0048] Bcl-6 (Oncoprotein); LEF/TCF (Lymphoid enhancer factor); P53 (Tumor suppressor); Ku70 (Autoantigen with multiple function, including DNA repair); H1F-1α (angiogenesis); GATA-1 (Transcription factor); WRN (Werner helicase); E2F-1 (Transcription factor); Smad7 (Transcription factor); Rb (Tumor suppressor); TFIIF (Transcription machinery); c-Jun (Transcription factor); α-Tubulin (Structural protein); HMGI(Y) (Chromatin structure); ACTR (Nuclear receptor coactivator); Androgen Receptor (Signal transduction); EKLF (Erythroid kruppel-like factor); YY-1 (Transcription factor); NF-κB(RelA) (Transcription factor); MyoD (Transcription factor); Importin a7 (Nuclear pore protein); Hsp90 (Chaperone protein); TFIIE (Transcription machinery); b-Catenin (Signaltransduction); TFJB (Transcription factor).

[0049] Genes whose transcription is altered by histone deacetylase inhibitors include:

[0050] 1) Genes that are induced by HDAC inhibitors: Cell cycle (p1 and cyclin E); Proapoptotic (Bak, BAX, CD95, and its ligand gelsolin, GADD45β, p53, Apaf-1 DFF45a, Bim, BAD, TRAIL, DR5, Fas and its ligand, and Caspase 9, -8 and -3); Redox Components (Thioredoxin-binding protein-1, thioredoxin, glutaredoxin and methallothionein 1L); Chromatin structure (Histone H2B); Retinoic acid pathway (RARβ).

[0051] 2) Genes that are repressed by HDAC inhibitors: Cell cycle (Cyclin D1 and A, and thymidylate synthase); Antiapoptotic (Bcl-2, Bcl-XL, c-FLIP, survivin, XIAP); Angiogenic factor (Vascular endothelial growth factor and HIF-Loc); Lipopolysaccharide-induced inflammatory cytokines (TNF-a, IFN-g and IL-1b and -6); Signaltransducer and activator of transcription 5- controlled genes (STAT5).

[0052] HDAC enzymes or isoforms appear to be involved in many different types of cancer. Inhibition of HDACs with HDAC inhibitors results in multiple and desirable anti-cancer effects such as, but not limited to, (i) the inhibition of cancer cell proliferation, (ii) the induction of apoptosis (cell death) of cancer cells, (iii) cell cycle regulation, (iv) the induction of tumour suppressor genes, and (v) the blocking of tumour angiogenesis (development of new tumour blood vessels). These multiple effects provided by HDAC inhibitors provide a method of treating cancer.

[0053] Interest in histone deacetylase enzymes (HDACs) as targets for pharmaceutical development has centered on the role of HDACs in regulating genes associated with cell-cycle progression and the development and progression of cancer (Kramer *et. al. Trends Endocrinol. Metab.* 12, 294-300, (2001)). Several studies have shown that treatment of various cell lines with HDAC inhibitors leads to hyper acetylation of histone proteins and cell-cycle arrest in late G_1 phase or at the G_2/M transition. Genes involved in the cell cycle that have been shown to be up regulated by HDAC inhibitors include p21, p27, p53 and cyclin E. Cyclin A and cyclin D have been reported to be down regulated by HDAC inhibitors. In tumor cell lines, several studies have shown that treatment with HDAC inhibitors lead to growth inhibition, growth arrest, terminal differentiation and/or apoptosis. In vivo studies have demonstrated growth inhibition of tumors and a reduction in tumor metastasis as a result of treatment with HDAC inhibitors.

[0054] The clearest link between abnormal HDAC activity and cancer occurs in acute promyelocytic leukemia. In this condition, a chromosomal translocation leads to the fusion of the retinoic acid receptor RARα with the promyelocytic leukemia (PML) or promyelocytic leukemia zinc-finger (PLZF) proteins. Both PML-RARα and PLZF-RARα promote the progression of leukemia by repressing retinoic acid-regulated genes through the abnormal recruitment of SMRT-mSin3-HDAC complex (Lin *et. al. Nature* 391, 811-814 (1998)); Grignani *et al. Nature*

391, 815-818 (1998)). Whereas the PML-RARα form of the disease is treatable with retinoic acid, the PLZF-RARα form is resistant to this treatment. For a patient with the retinoic acid-resistant form of the disease, the addition of the HDAC inhibitor sodium butyrate to the dosing regimen led to complete clinical and cytogenic remission (Warrell *et al. J. Natl. Cancer. Inst.* 90, 1621-1625, (1998)). HDACs have also been associated with Huntington's disease (Steffan, et al., *Nature* 413:739-744, "Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in Drosophila").

[0055] In general, almost all of the inhibitors targeting HDACs are broad spectrum compounds, inhibiting all of the HDAC isoforms with equal potency. These broad spectrum HDAC inhibitors cause the induction of differentiation, growth arrest and/or apoptosis in a large number of tumor cell lines *in vitro*.

[0056] Clinical administration of broad spectrum HDAC inhibitors (pan HDAC inhibitors) has been associated with many dose limiting toxicities. These include thrombocytopenia, and other hematological toxicities, QTc prolongation and other cardiac toxicities, nausea, fever, fatigue, and anorexia (For example, see *Clinical Cancer Research* **2003,** 9(10), 3578-3588; *Clinical Cancer Research* **2002,** *8(7)*, 2142-2148; and *Proceedings of the American Association of Cancer Research* **2005,** *46,* Abs 3978). Selective HDAC inhibitors that selectively inhibit only one HDAC isoform, as opposed to a pan-selective inhibitor, is expected to produce a drug with an improved toxicity profile.

[0057] Adverse effects in humans have been reported in several clinical trials using pan-HDAC inhibitors. Originally designed for oncological applications, such toxicities might not be crucial when taking into consideration their therapeutic effects and the high mortality rate of cancer.

[0058] Described herein are HDAC8 inhibitor compounds. Compounds described herein selectively inhibit HDAC8 over other HDAC isoforms (e.g. HDACs 1, 2, 3, 6, 10, and 11).

[0059] As described herein, HDAC8 is expressed primarily in delta cells of the islets of Langerhans in the pancreas; in small intestinal epithelial cells; and in neuroendocrine cells. Of note, delta cells express and secrete somatostatin, a peptide hormone that inhibits the secretion of insulin and growth hormone. Without being bound by theory, it is believed that HDAC8 activity drives the expression of somatostatin in delta cells. Thus, inhibiting HDAC8 activitity is expected to decrease somatostatin expression and secretion from delta cells, and consequently increase systemic insulin and growth hormone levels.

[0060] Described herein are methods for inhibiting somatostatin expression in a subject by administering to the subject a selective HDAC8 inhibitor composition. Further, described herein

are methods for treating a subject suffering from an insulin deficiency or a growth hormone deficiency by administering a selective HDAC8 inhibitor to the subject.

T-cell lymphomas or leukemias

[0061] HDAC8 is expressed at unusually high levels in tumor cell lines, e.g., Jurkat, HuT78, K562, PC3, and OVCR-3. In fact, as described herein, inhibiting HDAC8 activity decreases proliferation of T-cell derived tumor cells (e.g., Jurkat cells) by apoptosis. In contrast, HDAC8 inhibition does not affect the proliferation of either non-cancerous cells (e.g., peripheral blood mononuclear cells) or tumor cell lines other than T-cell derived lines. Thus, selective HDAC8 inhibitors are useful for slowing or arresting the progression of T-cell derived cancers with lessened or no toxicity to non-cancerous cells.

[0062] Described herein are methods for treating a subject suffering from a T-cell lymphoma by administering to the subject a selective HDAC8 inhibitor composition. Also described herein are methods for treating a subject suffering from a T-cell lymphoma by administering to the subject a population of autologous T-cells that have been exposed to a selective HDAC8 inhibitor composition *ex vivo*.

[0063] In some embodiments, selective HDAC8 inhibitor compounds and compositions thereof are used to treat a subject suffering from a T-cell lymphoma, e.g., a peripheral T-cell lymphoma, a lymphoblastic lymphoma, a cutaneous T-cell lymphoma, or an adult T-cell lymphoma.

[0064] In some embodiments, the T-cell lymphoma treatment method includes administering to a subject a therapeutically effective amount of a selective HDAC8 inhibitor pharmaceutical composition.

[0065] In other embodiments, the T-cell lymphoma treatment includes administering, in addition to a selective HDAC8 inhibitor pharmaceutical composition, one or more additional anti-cancer agents described herein in any combination.

[0066] The methods described herein include administering a pharmaceutical composition containing a selective HDAC8 inhibitor in a quantity sufficient to decrease HDAC8 deacetylase activity *in vivo* by a therapeutically effective amount. In some embodiments, cells derived from a subject to be treated (i.e. autologous cells) are exposed, *ex vivo*, to a pharmaceutical composition containing a selective HDAC8 inhibitor composition in a quantity sufficient to decrease HDAC8 deacetylase activity *in vitro*.

[0067] In one embodiment, T-cells from a donor subject suffering a T-cell lymphoma are cultured and expanded, *ex vivo*, in the presence of a selective HDAC8 inhibitor at a concentration that is effective for selectively killing transformed T-cells. Afterwards, the expanded T-cell population, free of transformed T-cells, are introduced into the donor subject.. T-cell culture, *in*

vitro expansion, and *in vivo* transfer is described in, e.g., Porter *et al.* (2006), *Blood*, 107(4):1325-1331; Rapoport *et al.* (2005), *Nat. Med.*, 1230-1237; Laport *et al.* (2003), *Blood*, 102(6):2004-2013.

Cytokine-Modulated Health Conditions

[0068] In some embodiments, a subject is administered a therapeutically effective amount of a selective HDAC8 inhibitor to decrease secretion of one or more inflammatory cytokines (e.g., IL-1β).

[0069] In some embodiments a selective HDAC8 inhibitor compound is administered to a subject to decrease the systemic levels of one or more inflammatory cytokines including, e.g., IL-1β, IL-6, IL-18, TNF-α, MCP-1, or MIP-1α.

[0070] As described herein, selective HDAC8 inhibitor compounds described herein reduce the secretion of proinflammatory cytokines including but not limited to interleukin-1 beta (IL-1β). Thus, HDAC8 is the HDAC enzyme involed in cytokine secretion. The use of selective HDAC8 inhibitor compounds provides a method of reducing cytokine secretion with reduced toxicity, due to the selective inhibition of one HDAC isoform (vs. the use of pan-HDAC inhibitors that inhibit all of the HDAC isoforms).

[0071] Selective HDAC8 inhibitor compounds described herein inhibit, in a dose dependent fashion, lipopolysaccharide (LPS) and/or ATP stimulated secretion of IL-1β from purified human peripheral blood mononuclear cells (PBMCs) as well as from the monocyte cell line THP-1. In some embodiments, the EC_{50} for inhibition ranges from about 0.5 micromolar to about 5 micromolar.

[0072] The production and secretion of IL-1β is via a non-classical pathway of protein secretion, involving potassium efflux, the autocatalytic processing of procaspase-1, the cleavage by active caspase-1 of the IL-1β precursor, the influx of calcium ions, and the activation of specific phospholipases including PLA-2. In some embodiments, selective HDAC8 inhibitor compounds described herein inhibit one or more steps in this secretory pathway.

[0073] As described herein, selective HDAC8 inhibitors are used to treat diseases or conditions that are mediated or linked to IL-1β secretion and activity. In certain autoimmune diseases or conditions, IL-1β is contributes to the signs and symptoms of the diseases or conditions (for examples of such Burger *et al.*, *Best Practice & Research Clinical Rheumatology*, Vol. 20, No. 5, pp. 879-896, 2006; Dayer *et al.*, *Current Opinions in Rheum.*, 2001, 13:170-176; Abramson *et al.*, *Rheumatology,* 2002; 41; 972-980); selective HDAC8 inhibitor compounds are used to treat such diseases or conditions. As described herein, selective HDAC8 inhibitor compounds are used to inhibit IL-1β secretion and thus find utility in the treatment of diseases or conditions that are

linked to IL-1β secretion and activity, which include, but are not limited to, osteoarthritis, rheumatoid arthritis, septic arthritis, gout, pseudogout, juvenile arthritis, Still's disease, Ankylosing spondylitis, systemic lupus erythematosus (SLE), Henoch-Schönlein purpura, psoriatic arthritis, reactive arthritis (Reiter's syndrome), hemochromatosis, hepatitis, Wegener's granulomatosis, Familial Mediterranean fever (FMF), HIDS (hyperimmunoglobulinemia D and periodic fever syndrome), TRAPS (TNF-alpha receptor associated periodic fever syndrome), inflammatory bowel disease, Crohn's Disease, ulcerative colitis, recurrent fever, anemia, leukocytosis, asthma, chronic obstructive pulmonary disease, myalgia; Adult Still's disease, Systemic-onset juvenile idiopathic arthritis, Lupus arthritis, Ankylosing spondylitis, familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), Blau syndrome, FCAS, MWS, neonatal-onset multisystem inflammatory disease (NOMID) and cryopyrin-associated periodic syndrome (CAPS), familial cold autoinflammatory syndrome (FCAS); Muckle-Wells syndrome (MWS); neonatal-onset multisystem inflammatory disease (NOMID); chronic infantile neurologic, cutaneous, articular syndrome (CINCA); cryopyrin-associated periodic syndrome (CAPS); pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome (PAPA).

[0074] In further embodiments, the methods described herein are used to treat an inflammatory disease, which includes, but is not limited to asthma, inflammatory bowel disease, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, and vulvitis.

[0075] In yet other embodiments, the methods described herein are used to treat an inflammatory skin condition. Inflammatory skin conditions are those conditions of the skin in which inflammatory cells (e.g., polymorphonuclear neutrophils and lymphocytes) infiltrate the skin with no overt or known infectious etiology. Symptoms of inflammatory skin conditions generally include erythema (redness), edema (swelling), pain, pruritus, increased surface temperature and loss of function. As used herein, inflammatory skin conditions include, but are not limited to, allergic contact dermatitis, urticarial dermatitis, psoriasis, eczema and related conditions, insect bites, erythroderma, mycosis fungoides and related conditions, pyoderma

gangrenosum, erythema multiforme, rosacea, onychomycosis, and acne and related conditions, but excluding psoriasis and its related conditions.

[0076] In some embodiments, the methods described herein are used to treat an autoimmune disease, which includes, but is not limited to, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, lupus, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease Sjögren's syndrome, multiple sclerosis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylitisis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, coeliac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behçet's disease, chronic fatigue, dysautonomia, endometriosis, interstitial cystitis, neuromyotonia, scleroderma, and vulvodynia.

[0077] In some embodiments, the methods described herein are used to treat heteroimmune conditions or diseases, which include, but are not limited to graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis.

[0078] Chronic inflammation in patients has been linked to cancer development (Coussens *et al.*, *Nature*, 420, 860-867, 2002). Cancers associated with chronic inflammation include, but are not limited to, lung, esophageal, gastric, pancreatic, cervical, bladder, prostate and colorectal cancers. The role of the inflammatory microenvironment as a causative factor in the etiology of cancer is also supported by findings that regular use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced incidence of colorectal, breast and gastric cancer. Pro-inflammatory cytokines are mediators of chronic inflammatory responses, and have effects on malignant processes.

[0079] Pro-inflammatory cytokines are involved in carcinogenesis and malignant transformation, tumor growth, invasion and metastasis. Persistent expression of proinflammatory cytokines, in or near tumors, exerts a range of effects, including but not limited to, increasing growth and invasiveness of the malignant cells, metastsis, tumorigenesis, to activation of immune-mediated mechanisms, leading to the destruction of tumor cells and inhibition of tumor growth. IL-1β -transfected tumor cells have been reported to fail to induce effective antitumor immune responses. In several human cancers, local IL-1β expression by the malignant cells or the microenvironment has been associated with aggressive tumor growth and poor prognosis.

[0080] In IL-1β -transfected fibrosarcoma cells, an up-regulation of MMP-2 and MMP-9 and TGFβ, genes that are involved in invasiveness, was observed, as opposed to the shut-off of these genes in IL-1α-transfected fibrosarcomas cells. IL-1β is thought to also enhance the invasiveness of already existing tumor cells by switching on angiogenesis and by the induction of inflammatory molecules, such as MMPs, heparanase, chemokines or integrins on the malignant cells or endothelial cells, leading to tumor dissemination and metastasis. IL-1β induces secretion of growth and invasiveness-promoting factors, e.g. matrix metalloproteinases and angiogenic factors (i.e. VEGF and bFGF and ELR-positive CXC chemokines, i.e. IL-8 and MCP-1). (Apte *et al.*, seminars in *Cancer Biology*, vol. 12, 2002, 277-290).

[0081] Secreted IL-1β has been implicated in tumor growth and invasion. Inhibition of IL-1β secretion, e.g. by using selective HDAC8 compounds, in malignant cells, or in the tumor's microenvironment provides a method for cancer therapy.

[0082] Thus in one embodiment, selective HDAC8 compounds described herein, are used in cancer therapy. In one embodiment, selective HDAC8 compounds described herein, are used in the treatment of sarcomas. In another embodiment, selective HDAC8 compounds described herein, are used in the treatment of sarcomas selected from among alveolar soft part sarcoma, angiosarcoma, dermatofibrosarcoma, desmoid tumor, desmoplastic small round cell tumor, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, hemangiopericytoma, hemangiosarcoma, kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, malignant fibrous histiocytoma, neurofibrosarcoma, rhabdomyosarcoma, synovial sarcoma, askin's tumor, ewing's, malignant hemangioendothelioma, malignant schwannoma, osteosarcoma, chondrosarcoma.

[0083] Symptoms, diagnostic tests, and prognostic tests for each of the above-mentioned conditions are known. See, e.g., "Harrison's Principles of Internal Medicine©," 16th ed., 2004, The McGraw-Hill Companies, Inc.

[0084] In various embodiments described herein, a subject suffers from more than one condition that is treated by administration of a therapeutically effective amount of a selective HDAC8 inhibitor composition. Thus, it is to be understood that the methods described herein are effective for treating a subject suffering from any combination of health conditions amenable to treatment by administration of a selective HDAC8 inhibitor composition. For example, in some embodiments, a subject suffering from a T-cell lymphoma also suffers from an inflammatory condition and *vice versa*.

Compounds

[0085] Compounds described herein, pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, or pharmaceutically acceptable solvates thereof, inhibit HDAC8 activity, and are used to treat patients where inhibition of HDAC8 activity provides benefit. Compounds described herein are HDAC8 inhibitor compounds.

[0086] In some embodiments of the methods described herein, the selective HDAC8 inhibitor has an IC_{50} for HDAC8 that is at least about 10 fold lower than the IC_{50} for HDAC1, HDAC2, HDAC3, HDAC6, HDAC10, or HDAC11. In some embodiments of any of the methods described herein, the selective HDAC8 inhibitor has an IC_{50} for HDAC8 that is less than about 100 nM and that is at least about 10 fold lower than the IC_{50} for HDAC1, HDAC2, HDAC3, HDAC6, HDAC10, or HDAC11. In some embodiments of any of the methods described herein, the selective HDAC8 inhibitor has an IC_{50} for HDAC8 that is less than about 50 nM and that is at least about 10 fold lower than the IC_{50} of the selective inhibitor for HDAC1, HDAC2, HDAC3, HDAC6, HDAC10, or HDAC11.

[0087] In some embodiments, selective HDAC8 inhibitors described herein have an IC_{50} for HDAC8 that is at least about 15 fold lower than the IC_{50} for HDAC1, HDAC2, HDAC3, HDAC6, and HDAC10. In some embodiments, selective HDAC8 inhibitors described herein have an IC_{50} for HDAC8 that is at least about 20 fold lower than the IC_{50} for HDAC1, HDAC2, HDAC3, HDAC6, and HDAC10. In some embodiments, selective HDAC8 inhibitors described herein have an IC_{50} for HDAC8 that is at least about 100 fold lower than the IC_{50} for HDAC1, HDAC2, HDAC3, HDAC6, and HDAC10. In addition, selective HDAC8 inhibitors described herein have an IC_{50} for HDAC8 that is less than about 100 nM while the IC_{50} for HDAC1, HDAC2, HDAC3, HDAC6, and HDAC10 is greater than about 100 nM.

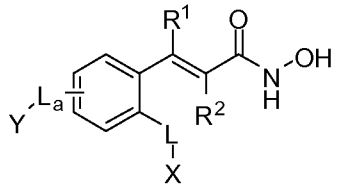
[0088] In some embodiments, selective HDAC8 inhibitors described herein have an IC_{50} for HDAC8 that is at least about 10 fold lower than the IC_{50} for HDAC1. In some embodiments, selective HDAC8 inhibitors described herein have an IC_{50} for HDAC8 that is at least about 20 fold lower than the IC_{50} for HDAC1. In some embodiments, selective HDAC8 inhibitors described herein have an IC_{50} for HDAC8 that is at least about 40 fold lower than the IC_{50} for HDAC1. In some embodiments, selective HDAC8 inhibitors described herein have an IC_{50} for HDAC8 that is at least about 100 fold lower than the IC_{50} for HDAC1. In some embodiments, selective HDAC8 inhibitors described herein have an IC_{50} for HDAC8 that is at least about 150 fold lower than the IC_{50} for HDAC1. In yet other embodiments, selective HDAC8 inhibitors

described herein have an IC_{50} for HDAC8 that is at least about 200 fold lower than the IC_{50} for HDAC1.

[0089] In some embodiments, selective HDAC8 inhibitors described herein have IC_{50} for HDAC8 that is less than about 100 nM and that is at least about 20 fold lower than the IC_{50} for other HDAC isoforms (HDAC1, HDAC2, HDAC3, HDAC6, HDAC10), wherein the IC_{50} for the other HDAC isoforms is greater than about 100 nM.

[0090] In one embodiment, described herein are selective histone deacetylase 8 (HDAC8) inhibitors. In one embodiment, the selective HDAC8 inhibitor has an IC_{50} for histone deacetylase 8 activity that is at least about 10 fold lower than the IC_{50} of the selective HDAC8 inhibitor for activity of histone deacetylase 1, histone deacetylase 2, histone deacetylase 3, histone deacetylase 6, histone deacetylase 10, or histone deacetylase 11.

[0091] In one aspect is a compound having a structure of Formula (I):



Formula (I);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

L and L_a are each independently a bond, O, S, NR^3, -$NR^{10}C(=O)$-R^{11}, S(=O), $S(=O)_2$, $NHS(=O)_2$, -C_1-C_6alkylene-, -C_2-C_6alkenylene-, -C_2-C_6alkynylene-, -C_1-C_6heteroalkylene-, -C_1-C_6alkylene-O-, -C_1-C_3alkylene-O-C_1-C_3alkylene-, -C_1-C_6alkylene-NR^3-, -C_1-C_3alkylene-NR^3-C_1-C_3alkylene -, -C_1-C_6alkylene-$C(=O)NR^3$-, -C_1-C_3alkylene-$C(=O)NR^3$-C_1-C_3alkylene -, -C_1-C_6alkylene-$NR^3C(=O)$-, -C_1-C_3alkylene-$NR^3C(=O)$-C_1-C_3alkylene-, -C_1-C_6alkylene-S-, -C_1-C_3alkylene-S-C_1-C_3alkylene-, -C_1-C_6alkylene-S(=O)-, -C_1-C_3alkylene-S(=O)-C_1-C_3alkylene, -C_1-C_6alkylene-$S(=O)_2$-, -C_1-C_3alkylene-$S(=O)_2$-C_1-C_3alkylene,–C(=O)-, or –C(=O)-C_1-C_6alkylene;

X is a substituted or unsubstituted group selected from among aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if X is substituted, then X is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -$NR^{10}C(=O)$-R^{11}, -C(=O)$N(R^{10})_2$, -$S(=O)_2N(R^{10})_2$, -$NR^{10}S(=O)_2$-R^{11}, -

$OC(=O)N(R^{10})_2$, $-NR^{10}C(=O)O-R^{11}$, $-OC(=O)O-R^{11}$, $-NHC(=O)NH-R^{11}$, $-OC(=O)-R^{11}$, $-N(R^{10})_2$, $-C_1-C_2alkylN(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

Y is H or a substituted or unsubstituted group selected from among C_1-C_6alkyl, $-CO_2R^{10}$, $-C(=O)R^{11}$, $-NR^{10}C(=O)-R^{11}$, $-C(=O)N(R^{10})_2$, aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if Y is substituted, then Y is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, $-NO_2$, $-CO_2R^{10}$, $-C(=O)R^{11}$, $-S-R^{11}$, $-S(=O)-R^{11}$, $-S(=O)_2-R^{11}$, $-NR^{10}C(=O)-R^{11}$, $-C(=O)N(R^{10})_2$, $-S(=O)_2N(R^{10})_2$, $-NR^{10}S(=O)_2-R^{11}$, $-OC(=O)N(R^{10})_2$, $-NR^{10}C(=O)O-R^{11}$, $-OC(=O)O-R^{11}$, $-NHC(=O)NH-R^{11}$, $-OC(=O)-R^{11}$, $-N(R^{10})_2$, $-C_1-C_2alkylN(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^3 is H, C_1-C_6alkyl, phenyl or benzyl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[0092] In one embodiment, is a substituted cinnamic acid hydroxyamide compound, wherein the substituent at the 2-position is L-X, wherein:

L is a bond, O, S, NR^3, S(=O), $S(=O)_2$, $-C_1-C_6$alkylene-, $-C_2-C_6$alkenylene-, $-C_2-C_6$alkynylene-, $-C_1-C_6$heteroalkylene-, $-C_1-C_6$alkylene-O-, $-C_1-C_3$alkylene-O-C_1-C_3alkylene-, $-C_1-C_6$alkylene-NR^3-, $-C_1-C_3$alkylene-NR^3-C_1-C_3alkylene -, $-C_1-C_6$alkylene-$C(=O)NR^3$-, $-C_1-C_3$alkylene-$C(=O)NR^3$-C_1-C_3alkylene -, $-C_1-C_6$alkylene-$NR^3C(=O)$-, $-C_1-C_3$alkylene-$NR^3C(=O)$-C_1-C_3alkylene-, $-C_1-C_6$alkylene-S-, $-C_1-C_3$alkylene-S-C_1-C_3alkylene-, $-C_1-C_6$alkylene-S(=O)-, $-C_1-C_3$alkylene-S(=O)-C_1-

C_3alkylene, -C_1-C_6alkylene-S(=O)$_2$-, -C_1-C_3alkylene-S(=O)$_2$-C_1-C_3alkylene,–C(=O)-, or –C(=O)-C_1-C_6alkylene;

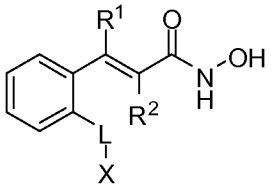
X is a substituted or unsubstituted group selected from among aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if X is substituted, then X is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -S(=O)$_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -S(=O)$_2$N(R^{10})$_2$, -NR^{10}S(=O)$_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

or an active metabolite, pharmaceutically acceptable solvate, pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[0093] For any and all embodiments, substituents are selected from among a subset of the listed alternatives. For example, in some embodiments, L is O, S, or NR^3. In other embodiments, L is O. In some embodiments, L is S. In some embodiments, L is NR^3 wherein R^3 is hydrogen. In one embodiment, L is NR^3 wherein R^3 is C_1-C_6alkyl. In another embodiment, L is NR^3 wherein R^3 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In another embodiment, L is NR^3 wherein R^3 is methyl. In yet another embodiment, L is a bond. In yet another embodiment, L is S(=O) or S(=O)$_2$. In another embodiment, L is -C_1-C_6alkylene-, -C_2-C_6alkenylene-, or -C_2-C_6alkynylene-. In yet another embodiment, L is C_1-C_6alkylene selected from methylene, ethylene or propylene. In another embodiment, L is -C_1-C_6heteroalkylene-, -C_1-C_6alkylene-O-, -C_1-C_3alkylene-O-C_1-C_3alkylene-, -C_1-C_6alkylene-NR^3-, -C_1-C_6alkylene-S-, -C_1-C_3alkylene-S-C_1-C_3alkylene-, or -C_1-C_3alkylene-NR^3-C_1-C_3alkylene-. In one embodiment, L is –CH_2-S-. In another embodiment, L is –CH_2NR^3-. In yet a further embodiment, L is –CH_2NR^3 wherein R^3 is H. In one embodiment, L is –CH_2-O-. In yet another embodiment, L is -C_1-C_6alkylene-C(=O)NR^3-, -C_1-C_3alkylene-C(=O)NR^3-C_1-C_3alkylene -, -C_1-C_6alkylene-NR^3C(=O)-, or -C_1-C_3alkylene-NR^3C(=O)-C_1-C_3alkylene-. In yet another embodiment, L is -C_1-C_6alkylene-S(=O)-, -C_1-C_3alkylene-S(=O)-C_1-C_3alkylene, -C_1-C_6alkylene-S(=O)$_2$-, -C_1-C_3alkylene-S(=O)$_2$-C_1-C_3alkylene. In yet a further embodiment, L is –C(=O)-, or –C(=O)-C_1-C_6alkylene.

[0094] Also described herein is a compound of Formula I(), wherein R^1 and R^2 are each independently H or C_1-C_6alkyl. In another embodiment, R^1 is H. In yet another embodiment, R^2 is H. In a further embodiment, both R^1 and R^2 are H. In yet a further embodiment, R^1 is C_1-C_6alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, or n-hexyl. In another embodiment, R^2 is C_1-C_6alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, or n-hexyl.

[0095] In another embodiment, is a compound of Formula (II):



Formula (II);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

L is a bond, O, S, NR^3, -$NR^{10}C(=O)$-R^{11}, S(=O), $S(=O)_2$, -C_1-C_6alkylene-, -C_2-C_6alkenylene-, -C_2-C_6alkynylene-, -C_1-C_6heteroalkylene-, -C_1-C_6alkylene-O-, -C_1-C_3alkylene-O-C_1-C_3alkylene-, -C_1-C_6alkylene-NR^3-, -C_1-C_3alkylene-NR^3-C_1-C_3alkylene -, -C_1-C_6alkylene-$C(=O)NR^3$-, -C_1-C_3alkylene-$C(=O)NR^3$-C_1-C_3alkylene -, -C_1-C_6alkylene-$NR^3C(=O)$-, -C_1-C_3alkylene-$NR^3C(=O)$-C_1-C_3alkylene-, -C_1-C_6alkylene-S-, -C_1-C_3alkylene-S-C_1-C_3alkylene-, -C_1-C_6alkylene-S(=O)-, -C_1-C_3alkylene-S(=O)-C_1-C_3alkylene, -C_1-C_6alkylene-$S(=O)_2$-, -C_1-C_3alkylene-$S(=O)_2$-C_1-C_3alkylene,–C(=O)-, or –C(=O)-C_1-C_6alkylene;

X is a substituted or unsubstituted group selected from among aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if X is substituted, then X is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -$NR^{10}C(=O)$-R^{11}, -C(=O)$N(R^{10})_2$, -$S(=O)_2N(R^{10})_2$, -$NR^{10}S(=O)_2$-R^{11}, -$OC(=O)N(R^{10})_2$, -$NR^{10}C(=O)O$-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -$N(R^{10})_2$, -C_1-C_2alkyl$N(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

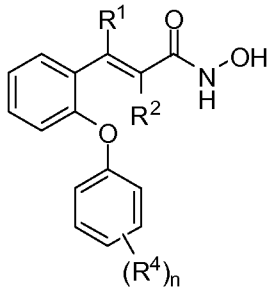
R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^3 is H, C_1-C_6alkyl, phenyl or benzyl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[0096] In another embodiment, is a compound of Formula (IIA):



Formula (IIA);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

R^4 is selected from among hydrogen, halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, $-NO_2$, $-CO_2R^{10}$, $-C(=O)R^{11}$, $-S-R^{11}$, $-S(=O)-R^{11}$, $-S(=O)_2-R^{11}$, $-NR^{10}C(=O)-R^{11}$, $-C(=O)N(R^{10})_2$, $-S(=O)_2N(R^{10})_2$, $-NR^{10}S(=O)_2-R^{11}$, $-OC(=O)N(R^{10})_2$, $-NR^{10}C(=O)O-R^{11}$, $-OC(=O)O-R^{11}$, $-NHC(=O)NH-R^{11}$, $-OC(=O)-R^{11}$, $-N(R^{10})_2$, $-C_1$-C_2alkyl$N(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

n is an integer from 0 to 5;

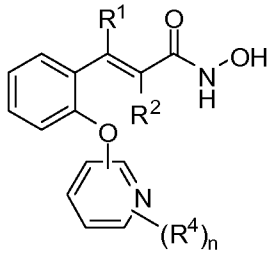
R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[0097] In one embodiment is a compound of Formula (IIA) wherein R^1 and R^2 are each independently H. In another embodiment is a compound of Formula (IIA) wherein R^4 is halogen. In another embodiment, R^4 is Cl. In a further embodiment, R^4 is F. In another embodiment, R^4 is Br. In another embodiment R^4 is C_1-C_6alkyl. In yet another embodiment, R^4 is methyl, ethyl, n-propyl, iso-propyl, iso-butyl, and tert-butyl. In a further embodiment, R^4 is methyl. In one embodiment, R^4 is C_1-C_6alkoxy. In another embodiment, R^4 is methoxy. In a further embodiment, R^4 is ethoxy. In another embodiment is a compound of Formula (IIA) wherein n is 1. In a further embodiment, n is 2. In yet a further embodiment R^4 is substituted para to the ether linker. In another embodiment, R^4 is substituted meta to the ether linker. In yet another embodiment, R^4 is substituted ortho to the ether linker.

[0098] In another embodiment, is a compound of Formula (IIB):



Formula (IIB);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

R^4 is selected from among hydrogen, halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -$S(=O)_2$N(R^{10})$_2$, -$NR^{10}S(=O)_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

n is an integer from 0 to 4;

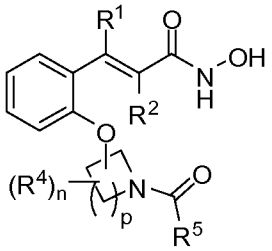
R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[0099] In one embodiment is a compound of Formula (IIB) wherein R^1 and R^2 are each independently H. In one embodiment is a compound of Formula (IIB) wherein R^4 is hydrogen. In another embodiment is a compound of Formula (IIB) wherein R^4 is halogen. In another embodiment, R^4 is Cl. In a further embodiment, R^4 is F. In another embodiment, R^4 is Br. In another embodiment R^4 is C_1-C_6alkyl. In yet another embodiment, R^4 is methyl, ethyl, n-propyl, iso-propyl, iso-butyl, and tert-butyl. In a further embodiment, R^4 is methyl. In one embodiment, R^4 is C_1-C_6alkoxy. In another embodiment, R^4 is methoxy. In a further embodiment, R^4 is ethoxy. In another embodiment is a compound of Formula (IIA) wherein n is 1. In a further embodiment, n is 2. In yet a further embodiment R^4 is substituted para to the ether linker. In another embodiment, R^4 is substituted meta to the ether linker. In yet another embodiment, R^4 is substituted ortho to the ether linker.

[00100] In another embodiment, is a compound of Formula (IIC):



Formula (IIC);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

R^4 and R^5 are each independently selected from among hydrogen, halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -S(=O)$_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -S(=O)$_2$N(R^{10})$_2$, -NR^{10}S(=O)$_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

p is an integer from 0 to 4;

n is an integer from 0 to 5;

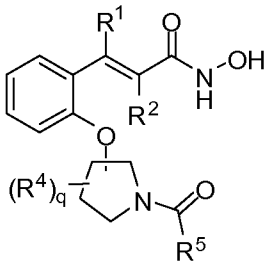
R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[00101] In one embodiment is a compound of Formula (IIC) wherein R^1 and R^2 are each independently H. In another embodiment is a compound of Formula (IIC) wherein p is 2. In another embodiment is a compound of Formula (IIC) wherein p is 3. In a further embodiment is a compound of Formula (IIC) wherein p is 4.

[00102] In one embodiment is a compound selected from Formula (IID):



Formula (IID);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

R^4 and R^5 are each independently selected from among hydrogen, halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -$S(=O)_2$N(R^{10})$_2$, -$NR^{10}S(=O)_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

q is an integer from 0 to 3;

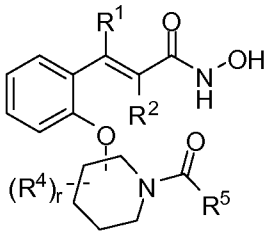
R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[00103] In one embodiment is a compound of Formula (IID) wherein q is 0. In another embodiment is a compound of Formula (IID) wherein R^1 and R^2 are each independently H. In a further embodiment is a compound of Formula (IID) wherein R^5 is C_1-C_6alkyl. In another embodiment, R^5 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In a further embodiment R^5 is methyl. In yet a further embodiment, R^5 is iso-propyl. In yet a further embodiment, R^5 is aryl. In another embodiment, R^5 is phenyl. In yet another embodiment, R^5 is heteroaryl. In one embodiment, R^5 is selected from pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, 4-azaindolyl, 5-azaindolyl, 6-azaindolyl, 7-azaindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl. In another embodiment, R^5 is pyridinyl. In a further embodiment, R^5 is furyl. In a further embodiment, R^5 is thienyl.

[00104] In another embodiment is a compound of Formula (IIE):



Formula (IIE);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

R^4 and R^5 are each independently selected from among hydrogen, halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -$S(=O)_2$N(R^{10})$_2$, -$NR^{10}S(=O)_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-

C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

r is an integer from 0 to 4;

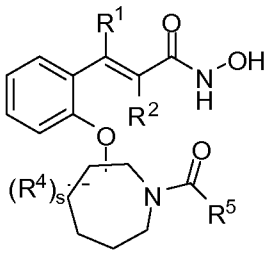
R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[00105] In one embodiment is a compound of Formula (IIE) wherein r is 0. In another embodiment is a compound of Formula (IIE) wherein R^1 and R^2 are each independently H. In a further embodiment is a compound of Formula (IIE) wherein R^5 is C_1-C_6alkyl. In another embodiment, R^5 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In a further embodiment R^5 is methyl. In yet a further embodiment, R^5 is aryl. In another embodiment, R^5 is phenyl. In yet another embodiment, R^5 is heteroaryl. In one embodiment, R^5 is selected from pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, 4-azaindolyl, 5-azaindolyl, 6-azaindolyl, 7-azaindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl. In another embodiment, R^5 is pyridinyl. In a further embodiment, R^5 is furyl. In a further embodiment, R^5 is thienyl.

[00106] In yet another embodiment is a compound of Formula (IIF):



Formula (IIF);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

R^4 and R^5 are each independently selected from among hydrogen, halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -$S(=O)_2$N(R^{10})$_2$, -NR^{10}S(=O)$_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

s is an integer from 0 to 5;

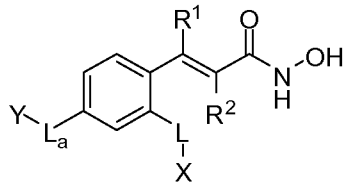
R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[00107] In one embodiment is a compound of Formula (IIF) wherein s is 0. In another embodiment is a compound of Formula (IIF) wherein R^1 and R^2 are each independently H. In a further embodiment is a compound of Formula (IIF) wherein R^5 is C_1-C_6alkyl. In another embodiment, R^5 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In a further embodiment R^5 is methyl. In yet a further embodiment, R^5 is aryl. In another embodiment, R^5 is phenyl. In yet another embodiment, R^5 is heteroaryl. In one embodiment, R^5 is selected from pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, 4-azaindolyl, 5-azaindolyl, 6-azaindolyl, 7-azaindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl. In another embodiment, R^5 is pyridinyl. In a further embodiment, R^5 is furyl. In a further embodiment, R^5 is thienyl.

[00108] In yet another embodiment is a compound of Formula (III):



Formula (III);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

L and L_a are each independently a bond, O, S, NR^3, -$NR^{10}C(=O)$-R^{11}, S(=O), $S(=O)_2$, $NHS(=O)_2$, -C_1-C_6alkylene-, -C_2-C_6alkenylene-, -C_2-C_6alkynylene-, -C_1-C_6heteroalkylene-, -C_1-C_6alkylene-O-, -C_1-C_3alkylene-O-C_1-C_3alkylene-, -C_1-C_6alkylene-NR^3-, -C_1-C_3alkylene-NR^3-C_1-C_3alkylene -, -C_1-C_6alkylene-$C(=O)NR^3$-, -C_1-C_3alkylene-$C(=O)NR^3$-C_1-C_3alkylene -, -C_1-C_6alkylene-$NR^3C(=O)$-, -C_1-C_3alkylene-$NR^3C(=O)$-C_1-C_3alkylene-, -C_1-C_6alkylene-S-, -C_1-C_3alkylene-S-C_1-C_3alkylene-, -C_1-C_6alkylene-S(=O)-, -C_1-C_3alkylene-S(=O)-C_1-C_3alkylene, -C_1-C_6alkylene-$S(=O)_2$-, -C_1-C_3alkylene-$S(=O)_2$-C_1-C_3alkylene,–C(=O)-, or –C(=O)-C_1-C_6alkylene;

X is a substituted or unsubstituted group selected from among aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if X is substituted, then X is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -$C(=O)R^{11}$, -S-R^{11}, -$S(=O)$-R^{11}, -$S(=O)_2$-R^{11}, -$NR^{10}C(=O)$-R^{11}, -$C(=O)N(R^{10})_2$, -$S(=O)_2N(R^{10})_2$, -$NR^{10}S(=O)_2$-R^{11}, -$OC(=O)N(R^{10})_2$, -$NR^{10}C(=O)O$-R^{11}, -$OC(=O)O$-R^{11}, -$NHC(=O)NH$-R^{11}, -$OC(=O)$-R^{11}, -$N(R^{10})_2$, -C_1-C_2alkyl$N(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

Y is H or a substituted or unsubstituted group selected from among C_1-C_6alkyl, -CO_2R^{10}, -$C(=O)R^{11}$, -$NR^{10}C(=O)$-R^{11}, -$C(=O)N(R^{10})_2$, aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if Y is substituted, then Y is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -

CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -S(=O)$_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -S(=O)$_2$N(R^{10})$_2$, -NR^{10}S(=O)$_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

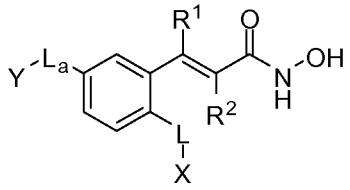
R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^3 is H, C_1-C_6alkyl, phenyl or benzyl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[00109] In yet another embodiment is a compound of Formula (IV):



Formula (IV);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

L and L_a are each independently a bond, O, S, NR^3, -NR^{10}C(=O)-R^{11}, S(=O), S(=O)$_2$, NHS(=O)$_2$, -C_1-C_6alkylene-, -C_2-C_6alkenylene-, -C_2-C_6alkynylene-, -C_1-C_6heteroalkylene-, -C_1-C_6alkylene-O-, -C_1-C_3alkylene-O-C_1-C_3alkylene-, -C_1-C_6alkylene-NR^3-, -C_1-C_3alkylene-NR^3-C_1-C_3alkylene -, -C_1-C_6alkylene-C(=O)NR^3-, -C_1-C_3alkylene-C(=O)NR^3-C_1-C_3alkylene -, -C_1-C_6alkylene-NR^3C(=O)-, -C_1-C_3alkylene-NR^3C(=O)-C_1-C_3alkylene-, -C_1-C_6alkylene-S-, -C_1-C_3alkylene-S-C_1-C_3alkylene-, -C_1-C_6alkylene-S(=O)-, -C_1-C_3alkylene-S(=O)-C_1-C_3alkylene, -C_1-C_6alkylene-S(=O)$_2$-, -C_1-C_3alkylene-S(=O)$_2$-C_1-C_3alkylene,–C(=O)-, or –C(=O)-C_1-C_6alkylene;

X is a substituted or unsubstituted group selected from among aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if X is substituted, then X is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-

C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -$S(=O)_2$N(R^{10})$_2$, -$NR^{10}S(=O)_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

Y is H or a substituted or unsubstituted group selected from among C_1-C_6alkyl, -CO_2R^{10}, -C(=O)R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, S(=O)$_2$-R^{11}, aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if Y is substituted, then Y is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -$S(=O)_2$N(R^{10})$_2$, -$NR^{10}S(=O)_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

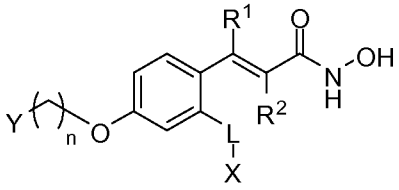
R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^3 is H, C_1-C_6alkyl, phenyl or benzyl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[00110] In another embodiment is a compound of Formula (III) wherein, L_a is a bond. In one embodiment, L_a is O. In a further embodiment, L_a is NH.

[00111] In another embodiment is a compound of Formula (IIIa) having the structure:



Formula (IIIa);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

L is a bond, O, S, NR^3, -$NR^{10}C(=O)$-R^{11}, S(=O), $S(=O)_2$, -C_1-C_6alkylene-, -C_2-C_6alkenylene-, -C_2-C_6alkynylene-, -C_1-C_6heteroalkylene-, -C_1-C_6alkylene-O-, -C_1-C_3alkylene-O-C_1-C_3alkylene-, -C_1-C_6alkylene-NR^3-, -C_1-C_3alkylene-NR^3-C_1-C_3alkylene -, -C_1-C_6alkylene-$C(=O)NR^3$-, -C_1-C_3alkylene-$C(=O)NR^3$-C_1-C_3alkylene -, -C_1-C_6alkylene-$NR^3C(=O)$-, -C_1-C_3alkylene-$NR^3C(=O)$-C_1-C_3alkylene-, -C_1-C_6alkylene-S-, -C_1-C_3alkylene-S-C_1-C_3alkylene-, -C_1-C_6alkylene-S(=O)-, -C_1-C_3alkylene-S(=O)-C_1-C_3alkylene, -C_1-C_6alkylene-$S(=O)_2$-, -C_1-C_3alkylene-$S(=O)_2$-C_1-C_3alkylene,–C(=O)-, or –C(=O)-C_1-C_6alkylene;

X is a substituted or unsubstituted group selected from among aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if X is substituted, then X is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -$C(=O)R^{11}$, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -$NR^{10}C(=O)$-R^{11}, -$C(=O)N(R^{10})_2$, -$S(=O)_2N(R^{10})_2$, -$NR^{10}S(=O)_2$-R^{11}, -$OC(=O)N(R^{10})_2$, -$NR^{10}C(=O)O$-R^{11}, -$OC(=O)O$-R^{11}, -NHC(=O)NH-R^{11}, -$OC(=O)$-R^{11}, -$N(R^{10})_2$, -C_1-C_2alkyl$N(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

Y is H or a substituted or unsubstituted group selected from among C_1-C_6alkyl, -CO_2R^{10}, -$C(=O)R^{11}$, -$NR^{10}C(=O)$-R^{11}, -$C(=O)N(R^{10})_2$, aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if Y is substituted, then Y is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -$C(=O)R^{11}$, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -$NR^{10}C(=O)$-R^{11}, -

$C(=O)N(R^{10})_2$, $-S(=O)_2N(R^{10})_2$, $-NR^{10}S(=O)_2-R^{11}$, $-OC(=O)N(R^{10})_2$, $-NR^{10}C(=O)O-R^{11}$, $-OC(=O)O-R^{11}$, $-NHC(=O)NH-R^{11}$, $-OC(=O)-R^{11}$, $-N(R^{10})_2$, $-C_1-C_2$alkyl$N(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

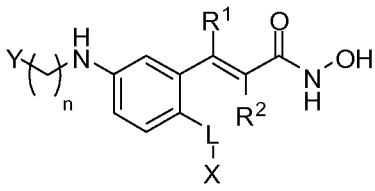
R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

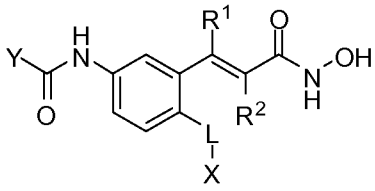
n is an integer from 0 to 4;

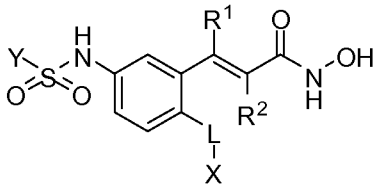
R^3 is H, C_1-C_6alkyl, phenyl or benzyl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[00112] In another embodiment is a compound having the structure:


Formula (IVa);


Formula (IVb);


Formula (IVc);

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

L is a bond, O, S, NR^3, $-NR^{10}C(=O)-R^{11}$, S(=O), $S(=O)_2$, $-C_1-C_6$alkylene-, $-C_2-C_6$alkenylene-, $-C_2-C_6$alkynylene-, $-C_1-C_6$heteroalkylene-, $-C_1-C_6$alkylene-O-, $-C_1-C_3$alkylene-O-C_1-C_3alkylene-, $-C_1-C_6$alkylene-NR^3-, $-C_1-C_3$alkylene-NR^3-C_1-C_3alkylene -, $-C_1-C_6$alkylene-$C(=O)NR^3$-, $-C_1-C_3$alkylene-$C(=O)NR^3$-C_1-C_3alkylene -, $-C_1-C_6$alkylene-$NR^3C(=O)$-, $-C_1-C_3$alkylene-$NR^3C(=O)-C_1-C_3$alkylene-, $-C_1-C_6$alkylene-S-, $-C_1-C_3$alkylene-S-C_1-C_3alkylene-, $-C_1-C_6$alkylene-S(=O)-, $-C_1-C_3$alkylene-S(=O)-C_1-C_3alkylene, $-C_1-C_6$alkylene-$S(=O)_2$-, $-C_1-C_3$alkylene-$S(=O)_2-C_1-C_3$alkylene,–C(=O)-, or –C(=O)-C_1-C_6alkylene;

X is a substituted or unsubstituted group selected from among aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if X is substituted, then X is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-

C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -$S(=O)_2$N(R^{10})$_2$, -$NR^{10}S(=O)_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

Y is H or a substituted or unsubstituted group selected from among C_1-C_6alkyl, -CO_2R^{10}, -C(=O)R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if Y is substituted, then Y is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -$S(=O)_2$N(R^{10})$_2$, -$NR^{10}S(=O)_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

n is an integer from 0 to 4;

R^3 is H, C_1-C_6alkyl, phenyl or benzyl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

[00113] In one embodiment is a compound of Formula (I), (II), (III), (IIIa), (IV), (IVa), (IVb), or (IVc), wherein X is a substituted or unsubstituted group selected from among aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if X is substituted, then X is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -

$C(=O)R^{11}$, $-S-R^{11}$, $-S(=O)-R^{11}$, $-S(=O)_2-R^{11}$, $-NR^{10}C(=O)-R^{11}$, $-C(=O)N(R^{10})_2$, $-S(=O)_2N(R^{10})_2$, $-NR^{10}S(=O)_2-R^{11}$, $-OC(=O)N(R^{10})_2$, $-NR^{10}C(=O)O-R^{11}$, $-OC(=O)O-R^{11}$, $-NHC(=O)NH-R^{11}$, $-OC(=O)-R^{11}$, $-N(R^{10})_2$, $-C_1-C_2alkylN(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[00114] In some embodiments is a compound of Formula (I), (II), (III), (IIIa), (IV), (IVa), (IVb), or (IVc), wherein X is a substituted or unsubstituted aryl group. In another embodiment, X is a substituted or unsubstituted phenyl group. In yet another embodiment, X is a substituted or unsubstituted naphthalene group. In yet a further embodiment, X is an unsubstituted phenyl group.

[00115] In some embodiments, X is selected from among phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3,4-dimethylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3,4-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,5-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-(trifluoromethyl)-phenyl, 3-(trifluoromethyl)-phenyl, 4-(trifluoromethyl)-phenyl, 2-(trifluoromethoxy)-phenyl, 3-(trifluoromethoxy)-phenyl, 4-(trifluoromethoxy)-phenyl, 2-chloro-4-fluorophenyl, 3-chloro-4-fluorophenyl, 2-fluoro-4-chlorophenyl, 3-fluoro-4-cholorophenyl, 2-chloro-4-methoxyphenyl, 2,3-dichlorophenyl, 3-methoxy-4-fluorophenyl, 3-methoxy-5-fluorophenyl, 3-methoxy-4-chlorophenyl, 3-(methylsulfonyl)phenyl, 4-(methylsulfonyl)phenyl, 2-thiophenyl, 3-thiophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3-fluoro-4-methoxy-phenyl, 2-(difluoromethoxy)-phenyl, 3-(difluoromethoxy)-phenyl, 4-(difluoromethoxy)-phenyl, N-methylsulfonyl-2-aminophenyl, N-methylsulfonyl-3-aminophenyl, N-methylsulfonyl-4-aminophenyl, N-phenylsulfonyl-2-aminophenyl, N-phenylsulfonyl-3-aminophenyl, N-phenylsulfonyl-4-aminophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2-dimethylaminophenyl, 3-dimethylaminophenyl, 4-dimethylaminophenyl, N-acetyl-2-aminophenyl, N-acetyl-3-aminophenyl, N-acetyl-4-aminophenyl, N-benzoyl-2-aminophenyl, N-benzoyl-3-aminophenyl, and N-benzoyl-4-aminophenyl.

[00116] In other embodiments, X is selected from among phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-fluoro-4methoxyphenyl, 4-(trifluoromethoxy)-phenyl, 3,4-dichlorophenyl, 2,4-dichlorophenyl, 2-chloro-4-fluorophenyl, 3-chloro-4-fluorophenyl, 2-fluoro-4-chlorophenyl, 3-fluoro-4-cholorophenyl, 2-chloro-4-methoxyphenyl, 2,3-dichlorophenyl, 3-methoxy-4-fluorophenyl, 3-methoxy-5-

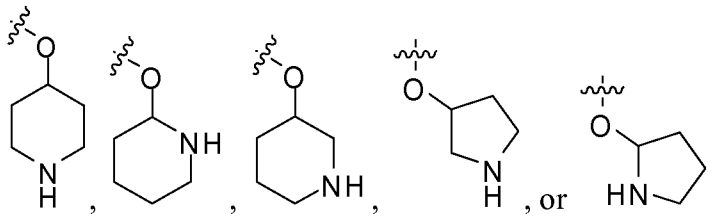
fluorophenyl, 3-methoxy-4-chlorophenyl, 3-(methylsulfonyl)phenyl, 4-(methylsulfonyl)phenyl, 2-thiophenyl, 3-thiophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, and 3,4-difluorophenyl.

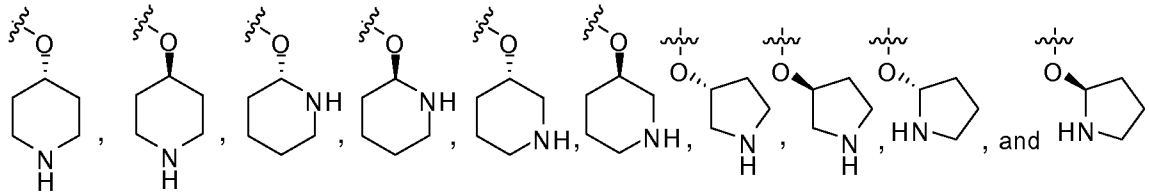
[00117] In another embodiment is a compound of Formula (I), (II), (III), (IIIa), (IV), (IVa), (IVb), or (IVc), wherein X is a substituted or unsubstituted heteroaryl. In one embodiment X is heteroaryl selected from pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, 4-azaindolyl, 5-azaindolyl, 6-azaindolyl, 7-azaindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl. In one embodiment, X is a substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl. In another embodiment, 2-pyridyl, 3-pyridyl, 4-pyridyl are each independently substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -$S(=O)_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)$N(R^{10})_2$, -$S(=O)_2N(R^{10})_2$, -$NR^{10}S(=O)_2$-R^{11}, -OC(=O)$N(R^{10})_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -$N(R^{10})_2$, -C_1-C_2alkyl$N(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In a further embodiment, 2-pyridyl, 3-pyridyl, 4-pyridyl are each independently substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, and -S-R^{11}. In one embodiment, halogen is Cl. In another embodiment, halogen is Br. In a further embodiment, halogen is F. In yet a further embodiment, 2-pyridyl, 3-pyridyl, 4-pyridyl are each independently substituted with CN. In yet another embodiment, 2-pyridyl, 3-pyridyl, 4-pyridyl are each independently substituted with OH. In yet a further embodiment, 2-pyridyl, 3-pyridyl, 4-pyridyl are each independently substituted with at least two substituents. In a further embodiment, 2-pyridyl, 3-pyridyl, 4-pyridyl are each independently substituted with at least three substituents.

[00118] Also described herein is a compound of Formula (I), (II), (III), (IIIa), (IV), (IVa), (IVb), or (IVc), wherein X is a substituted or unsubstituted C_3-C_8cycloalkyl. In one embodiment C_3-C_8cycloalkyl is selected from cyclopentyl, cyclohexyl, and cycloheptyl. In one embodiment, cyclopentyl, cyclohexyl, and cycloheptyl are each independently substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-

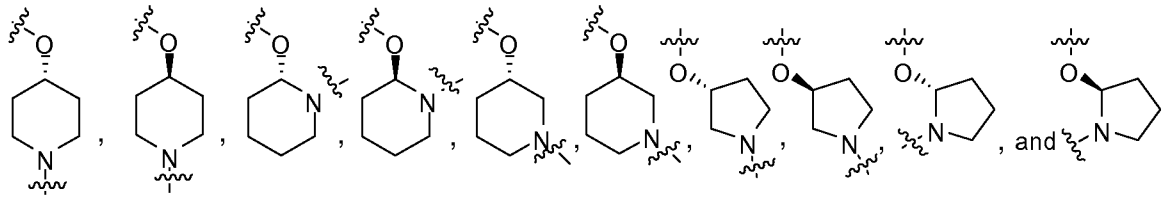
C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -S(=O)$_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -S(=O)$_2$N(R^{10})$_2$, -NR^{10}S(=O)$_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In a further embodiment, cyclopentyl, cyclohexyl, and cycloheptyl are each independently substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, and -S-R^{11}. In one embodiment, halogen is Cl. In another embodiment, halogen is Br. In a further embodiment, halogen is F. In yet a further embodiment, cyclopentyl, cyclohexyl, and cycloheptyl are each independently substituted with CN. In yet another embodiment, cyclopentyl, cyclohexyl, and cycloheptyl are each independently substituted with OH. In yet a further embodiment, cyclopentyl, cyclohexyl, and cycloheptyl are each independently substituted with at least two substituents. In a further embodiment, cyclopentyl, cyclohexyl, and cycloheptyl are each independently substituted with at least three substituents.

[00119] In one embodiment is a compound of Formula (I), (II), (III), (IIIa), (IV), (IVa), (IVb), or (IVc), wherein X is substituted or unsubstituted C_2-C_{10}heterocycloalkyl selected from quinolizinyl, dioxinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiazinyl, tetrahydropyridinyl, piperazinyl, oxazinanonyl, dihydropyrrolyl, dihydroimidazolyl, tetrahydrofuranyl, tetrahydropyranyl, dihydrooxazolyl, oxiranyl, pyrrolidinyl, pyrazolidinyl, dihydrothienyl, imidazolidinonyl, pyrrolidinonyl, dihydrofuranonyl, dioxolanonyl, thiazolidinyl, piperidinonyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and tetrahydrothienyl. In one embodiment, X is substituted or unsubstituted piperidinyl or pyrrolidine. In one embodiment, is a compound of Formula (I), (II), (III), (IIIa), (IV), (IVa), (IVb), or (IVc), wherein L-X is O-piperidinyl or O-pyrrolidine wherein piperidinyl or pyrrolidine is optionally substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -C(=O)R^{11}, -S-R^{11}, -S(=O)-R^{11}, -S(=O)$_2$-R^{11}, -NR^{10}C(=O)-R^{11}, -C(=O)N(R^{10})$_2$, -S(=O)$_2$N(R^{10})$_2$, -NR^{10}S(=O)$_2$-R^{11}, -OC(=O)N(R^{10})$_2$, -NR^{10}C(=O)O-R^{11}, -OC(=O)O-R^{11}, -NHC(=O)NH-R^{11}, -OC(=O)-R^{11}, -N(R^{10})$_2$, -C_1-C_2alkylN(R^{10})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

In one embodiment, L-X is  . In another embodiment, L-X is selected from



wherein X is an unsubstituted piperidine or pyrrolidine. In another embodiment, L-X is



wherein X is a substituted piperidine or pyrrolidine moiety wherein the substitution is at the nitrogen atom.

[00120] In an further embodiment, the piperidine or pyrrolidine is substituted at the nitrogen atom with $-C(=O)R^{11}$ wherein R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl. In another embodiment, the piperidine or pyrrolidine is substituted at the nitrogen atom with $-C(=O)R^{11}$ wherein R^{11} is substituted or unsubstituted C_1-C_6alkyl. In one embodiment, R^{11} is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl. In another embodiment, R_{11} is methyl. In yet another embodiment, R_{11} is iso-propyl.

[00121] In another embodiment, the piperidine or pyrrolidine is substituted at the nitrogen atom with $-C(=O)R^{11}$ wherein R^{11} is a substituted or unsubstituted aryl. In one embodiment, the substituted or unsubstituted aryl is a phenyl group. In another embodiment, the substituted or unsubstituted aryl group is a naphthalene group. In yet another embodiment, the piperidine or pyrrolidine is substituted at the nitrogen atom with $-C(=O)R^{11}$ wherein R^{11} is a phenyl substituted with at least one group selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, $-NO_2$, $-CO_2R^{12}$, $-C(=O)R^{13}$, $-S-R^{13}$, $-S(=O)-R^{13}$, $-S(=O)_2-R^{13}$, $-NR^{12}C(=O)-R^{13}$, $-C(=O)N(R^{12})_2$, $-S(=O)_2N(R^{12})_2$, $-NR^{12}S(=O)_2-R^{13}$, $-OC(=O)N(R^{12})_2$, $-NR^{12}C(=O)O-R^{13}$, $-OC(=O)O-R^{13}$, $-NHC(=O)NH-R^{13}$, $-OC(=O)-R^{13}$, $-N(R^{12})_2$, $-C_1$-C_2alkyl$N(R^{12})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-

C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein R^{12} is hydrogen, C_1-C_6alkyl, phenyl or benzyl and R^{13} is C_1-C_6alkyl, phenyl or benzyl. In another embodiment, R^{11} is a phenyl substituted with a halogen. In another embodiment, R^{11} is a phenyl substituted with a substituent selected from –CN, -NO_2 or SH.

[00122] In another embodiment, the piperidine or pyrrolidine is substituted at the nitrogen atom with –C(=O)R^{11} wherein R^{11} is a substituted or unsubstituted heteroaryl. In one embodiment, the substituted or unsubstituted heteroaryl is pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, 4-azaindolyl, 5-azaindolyl, 6-azaindolyl, 7-azaindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl. In another embodiment, the substituted or unsubstituted group is pyridinyl. In yet another embodiment, the piperidine or pyrrolidine is substituted at the nitrogen atom with –C(=O)R^{11} wherein R^{11} is a pyridine substituted with at least one group selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{12}, -C(=O)R^{13}, -S-R^{13}, -S(=O)-R^{13}, -S(=O)$_2$-R^{13}, -NR^{12}C(=O)-R^{13}, -C(=O)N(R^{12})$_2$, -S(=O)$_2$N(R^{12})$_2$, -NR^{12}S(=O)$_2$-R^{13}, -OC(=O)N(R^{12})$_2$, -NR^{12}C(=O)O-R^{13}, -OC(=O)O-R^{13}, -NHC(=O)NH-R^{13}, -OC(=O)-R^{13}, -N(R^{12})$_2$, -C_1-C_2alkylN(R^{12})$_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein R^{12} is hydrogen, C_1-C_6alkyl, phenyl or benzyl and R^{13} is C_1-C_6alkyl, phenyl or benzyl. In another embodiment, R^{11} is a 2-pyridine, 3-pyridine or 4-pyridine. In yet a further embodiment, the heteroaryl is substituted with a halogen. In another embodiment, R^{11} is a 2-pyridine, 3-pyridine, or 4-pyridine substituted with a substituent selected from –CN, -NO_2 or SH. In a further embodiment, the heteroaryl is selected from furan, thiophene, benzothiazole, benzoxazole, oxadiazole, or oxazole. In yet a further embodiment, the heteroaryl is furan optionally substituted with a halogen, C_1-C_6alkyl or OH.

[00123] In a further embodiment is a compound of Formula (I), (III), (IIIa), (IV), (IVa), (IVb), or (IVc), wherein Y is a substituted or unsubstituted aryl. In one embodiment, Y is a substituted phenyl. In a further embodiment, Y is a phenyl group. In one embodiment, the phenyl is substituted with at least one halogen. In another embodiment, the phenyl is substituted with at

least two halogen groups. In a further embodiment, the phenyl group is substituted with a F group. In another embodiment, the phenyl group is substituted with at least one Cl. In another embodiment, with two Cl groups.

[00124] In yet another embodiment is a compound of Formula (I), (III), (IIIa), (IV), (IVa), (IVb), or (IVc), wherein Y is a substituted or unsubstituted heteroaryl. In one embodiment the unsubstituted or substituted heteroaryl group is selected from pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, 4-azaindolyl, 5-azaindolyl, 6-azaindolyl, 7-azaindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl.

[00125] In one embodiment is a compound of Formula (I), (III), (IIIa), (IV), (IVa), (IVb), or (IVc), wherein Y is pyridine. In another embodiment, Y is pyrimidine. In a further embodiment, Y is furan. In another embodiment, Y is thiophene. In a further embodiment, Y is indole.

[00126] In another embodiment is a compound of Formula (I), (III), (IIIa), (IV), (IVa), (IVb), or (IVc), wherein Y is substituted or unsubstituted C_2-C_{10}heterocycloalkyl. In another embodiment, the C_2-C_{10} heterocycloalkyl is selected from quinolizinyl, dioxinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiazinyl, tetrahydropyridinyl, piperazinyl, oxazinanonyl, dihydropyrrolyl, dihydroimidazolyl, tetrahydrofuranyl, tetrahydropyranyl, dihydrooxazolyl, oxiranyl, pyrrolidinyl, pyrazolidinyl, dihydrothienyl, imidazolidinonyl, pyrrolidinonyl, dihydrofuranonyl, dioxolanonyl, thiazolidinyl, piperidinonyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and tetrahydrothienyl.

[00127] In one embodiment is a compound of Formula (I), (III), (IIIa), (IV), (IVa), (IVb), or (IVc), wherein Y is substituted or unsubstituted piperazine. In another embodiment, piperazine is substituted with C_1-C_6alkyl. In a further embodiment, C_1-C_6alkyl is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, or tert-butyl. In another embodiment, piperazine is substituted with methyl.

[00128] Any combination of the groups described above for the various variables is contemplated herein. It is understood that substituents and substitution patterns on the compounds provided herein are selected to provide compounds that are chemically stable and that are synthesized by techniques set forth herein.

[00129] Throughout the specification, groups and substituents thereof are chosen to provide stable moieties and compounds.

Further Forms of Compounds

[00130] In some embodiments, compounds described herein possess one or more stereocenters and each center exists in the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. In some embodiments, separation of steroisomers are performed by chromatography. In other embodiments, individual stereoisomers are obtained by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In one embodiment the resolution of enantiomers are carried out using covalent diastereomeric derivatives of the compounds described herein, dissociable complexes are also possible (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are readily separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer(s) is/are then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture is found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981, herein incorporated by reference for such disclosure. In further embodiments, tereoisomers are obtained by stereoselective synthesis.

[00131] In some situations, compounds exist as tautomers. All tautomers are included within the formulas described herein.

[00132] The methods and formulations described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds described herein, as well as active metabolites of these compounds having the same type of activity. In some situations, compounds exist as tautomers. All tautomers are included within the scope of the compounds presented herein. In addition, the compounds described herein exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00133] In some embodiments, the compounds described herein in unoxidized form are prepared from the corresponding N-oxides compounds by treating with a reducing agent, such as, but not limited to, sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, phosphorus tribromide, or the like in a suitable inert organic

solvent, such as, but not limited to, acetonitrile, ethanol, aqueous dioxane, or the like at 0 to 80°C.

[00134] In some embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. In some embodiments, prodrugs are bioavailable by oral administration whereas the parent is not. In other embodiments, the prodrug has improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound described herein, which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug is a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

[00135] To produce a prodrug, a pharmaceutically active compound is modified such that the active compound will be regenerated upon *in vivo* administration. In some embodiments, the prodrug is designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. In some embodiments, once a pharmaceutically active compound is known, knowledge of pharmacodynamic processes and drug metabolism *in vivo,* aids in the design of prodrugs of the compound. (see, for example, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392; Silverman (1992), The Organic Chemistry of Drug Design and Drug Action, Academic Press, Inc., San Diego, pages 352-401, Saulnier *et al.*, (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985; Rooseboom *et al.*, *Pharmacological Reviews*, 56:53–102, 2004; Miller *et al.*, *J. Med. Chem.* Vol.46, no. 24, 5097-5116, 2003; Aesop Cho, "Recent Advances in Oral Prodrug Discovery", *Annual Reports in Medicinal Chemistry*, Vol. 41, 395-407, 2006).

[00136] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a derivative as set forth herein are included within the scope of the claims. In some embodiemtns, some of the herein-described compounds are a prodrug for another derivative or active compound.

[00137] In some embodiments prodrugs are easier to administer than the parent drug. In some embodiments the prodrug is bioavailable by oral administration whereas the parent is not. In other embodiments the prodrug has improved solubility in pharmaceutical compositions over the parent drug. In further embodiments, prodrugs are designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. In some embodiments, the design of a prodrug increases the effective water solubility. See, e.g., Fedorak *et al.*, *Am. J. Physiol.*, 269:G210-218 (1995); McLoed *et al.*, *Gastroenterol*, 106:405-413 (1994); Hochhaus *et al.*, *Biomed. Chrom.,* 6:283-286 (1992); J. Larsen and H. Bundgaard, *Int. J. Pharmaceutics,* 37, 87 (1987); J. Larsen et al., *Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula et al., *J. Pharm. Sci.*, 64:181-210 (1975); T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, all incorporated herein for such disclosure.

[00138] Sites on the aromatic ring portion of compounds described herein are susceptible to various metabolic reactions, therefore incorporation of appropriate substituents on the aromatic ring structures, such as, by way of example only, halogens reduces, minimizes or eliminates this metabolic pathway.

[00139] In some embodiments the compounds described herein are labeled isotopically (e.g. with a radioisotope) or by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00140] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, respectively. Certain isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Further, substitution with isotopes such as deuterium, i.e., ^{2}H, afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements.

[00141] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

[00142] In some embodiments, compounds described herein are formed as, and/or used as, pharmaceutically acceptable salts. The type of pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic acid, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, metaphosphoric acid, and the like; or with an organic acid, such as, for example, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, trifluoroacetic acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1 -carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion (e.g. lithium, sodium, potassium), an alkaline earth ion (e.g. magnesium, or calcium), or an aluminum ion. In some embodiments, compounds described herein form a coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other embodiments, compounds described herein form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

[00143] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and form during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[00144] In some embodiments, compounds described herein are in various forms, including but not limited to, amorphous forms, milled forms and nano-particulate forms. In addition, compounds described herein include crystalline forms, also known as polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. In some embodiments, various factors such as the recrystallization solvent, rate of crystallization, and storage temperature cause a single crystal form to dominate.

[00145] In other embodiments, the screening and characterization of the pharmaceutically acceptable salts, polymorphs and/or solvates is accomplished by using a variety of techniques including, but not limited to, thermal analysis, x-ray diffraction, spectroscopy, vapor sorption, and microscopy. Thermal analysis methods address thermo chemical degradation or thermo physical processes including, but not limited to, polymorphic transitions, and such methods are used to analyze the relationships between polymorphic forms, determine weight loss, to find the glass transition temperature, or for excipient compatibility studies. Such methods include, but are not limited to, Differential scanning calorimetry (DSC), Modulated Differential Scanning Calorimetry (MDCS), Thermogravimetric analysis (TGA), and Thermogravi-metric and Infrared analysis (TG/IR). X-ray diffraction methods include, but are not limited to, single crystal and powder diffractometers and synchrotron sources. The various spectroscopic techniques used include, but are not limited to, Raman, FTIR, UV-VIS, and NMR (liquid and solid state). The various microscopy techniques include, but are not limited to, polarized light microscopy, Scanning Electron Microscopy (SEM) with Energy Dispersive X-Ray Analysis (EDX), Environmental Scanning Electron Microscopy with EDX (in gas or water vapor atmosphere), IR microscopy, and Raman microscopy.

[00146] Throughout the specification, groups and substituents thereof are chosen to provide stable moieties and compounds.

Synthesis of Compounds

[00147] The synthesis of compounds described herein are accomplished using means described in the chemical literature, using the methods described herein, or by a combination thereof. In addition, solvents, temperatures and other reaction conditions presented herein vary according to the means described in the chemical literature, using the methods described herein, or by a combination thereof.

[00148] The starting materials and reagents used for the synthesis of the compounds described herein are synthesized or are obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Fluka, Acros Organics, Alfa Aesar, Bachem and the like.

[00149] The compounds described herein, and other related compounds having different substituents are synthesized using techniques and materials described herein and as described, for example, in Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989), March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999) (all of which are incorporated by reference for such disclosure). General methods for the preparation of compound as disclosed herein are modified by the use of appropriate reagents and conditions, for the introduction of the various moieties found in the formulae as provided herein. As a guide the following synthetic methods are utilized.

[00150] Compounds described herein are synthesized starting from compounds that are available from commercial sources or that are prepared using procedures outlined herein.

[00151] Using the reaction conditions described herein, cinnamic acid hydroxamate compositions as disclosed herein are obtained in good yields and purity. The compounds prepared by the methods disclosed herein are purified by conventional means such as, filtration, recrystallization, chromatography, distillation, and combinations thereof.

[00152] Schemes presented herein are merely illustrative of some methods by which the compounds described herein are synthesized, and various modifications to these schemes are made based on this disclosure.

Formation of Covalent Linkages by Reaction of an Electrophile with a Nucleophile

[00153] The compounds described herein are modified using various electrophiles and/or nucleophiles to form new functional groups or substituents. Table A entitled "Examples of Covalent Linkages and Precursors Thereof" lists selected non-limiting examples of covalent linkages and precursor functional groups which yield the covalent linkages. Table A is used as guidance toward the variety of electrophiles and nucleophiles combinations available that provide covalent linkages. Precursor functional groups are shown as electrophilic groups and nucleophilic groups.

Table A: Examples of Covalent Linkages and Precursors Thereof

Covalent Linkage Product	Electrophile	Nucleophile
Carboxamides	Activated esters	amines/anilines
Carboxamides	acyl azides	amines/anilines
Carboxamides	acyl halides	amines/anilines
Esters	acyl halides	alcohols/phenols
Esters	acyl nitriles	alcohols/phenols
Carboxamides	acyl nitriles	amines/anilines
Imines	Aldehydes	amines/anilines
Hydrazones	aldehydes or ketones	Hydrazines
Oximes	aldehydes or ketones	Hydroxylamines
Alkyl amines	alkyl halides	amines/anilines
Esters	alkyl halides	carboxylic acids
Thioethers	alkyl halides	Thiols
Ethers	alkyl halides	alcohols/phenols
Thioethers	alkyl sulfonates	Thiols
Esters	alkyl sulfonates	carboxylic acids
Ethers	alkyl sulfonates	alcohols/phenols
Esters	Anhydrides	alcohols/phenols
Carboxamides	Anhydrides	amines/anilines
Thiophenols	aryl halides	Thiols
Aryl amines	aryl halides	Amines
Thioethers	Azindines	Thiols
Boronate esters	Boronates	Glycols
Carboxamides	carboxylic acids	amines/anilines
Esters	carboxylic acids	Alcohols
Hydrazines	Hydrazides	carboxylic acids
N-acylureas or Anhydrides	carbodiimides	carboxylic acids
Esters	diazoalkanes	carboxylic acids
Thioethers	Epoxides	Thiols
Thioethers	haloacetamides	Thiols
Ammotriazines	halotriazines	amines/anilines
Triazinyl ethers	halotriazines	alcohols/phenols

Amidines	imido esters	amines/anilines
Ureas	Isocyanates	amines/anilines
Urethanes	Isocyanates	alcohols/phenols
Thioureas	isothiocyanates	amines/anilines
Thioethers	Maleimides	Thiols
Phosphite esters	phosphoramidites	Alcohols
Silyl ethers	silyl halides	Alcohols
Alkyl amines	sulfonate esters	amines/anilines
Thioethers	sulfonate esters	Thiols
Esters	sulfonate esters	carboxylic acids
Ethers	sulfonate esters	Alcohols
Sulfonamides	sulfonyl halides	amines/anilines
Sulfonate esters	sulfonyl halides	phenols/alcohols

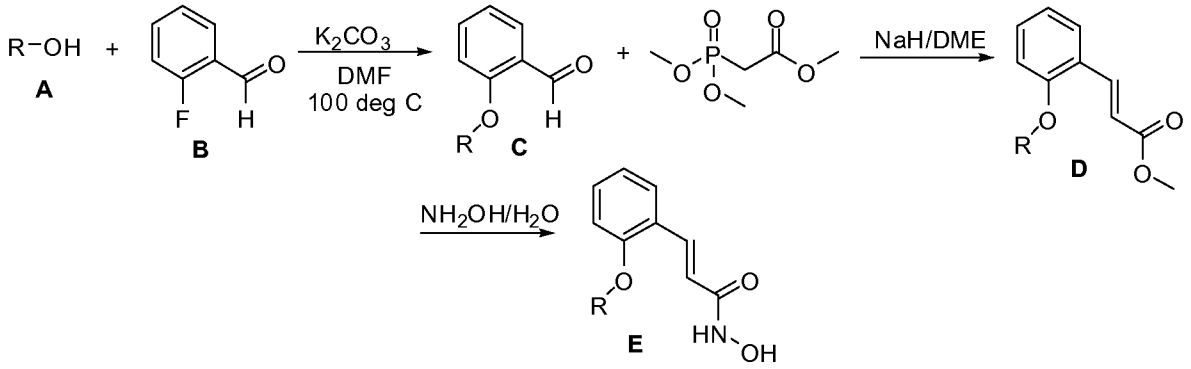
[00154] In the reactions described, it is necessary in certain cases to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Protecting groups are used to block some or all reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. In one embodiment, each protective group is removable by a different means. Protecting groups, plus a detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference for such disclosure.

General Syntheses

Cinnamic Acid Hydroxyamide Compounds:

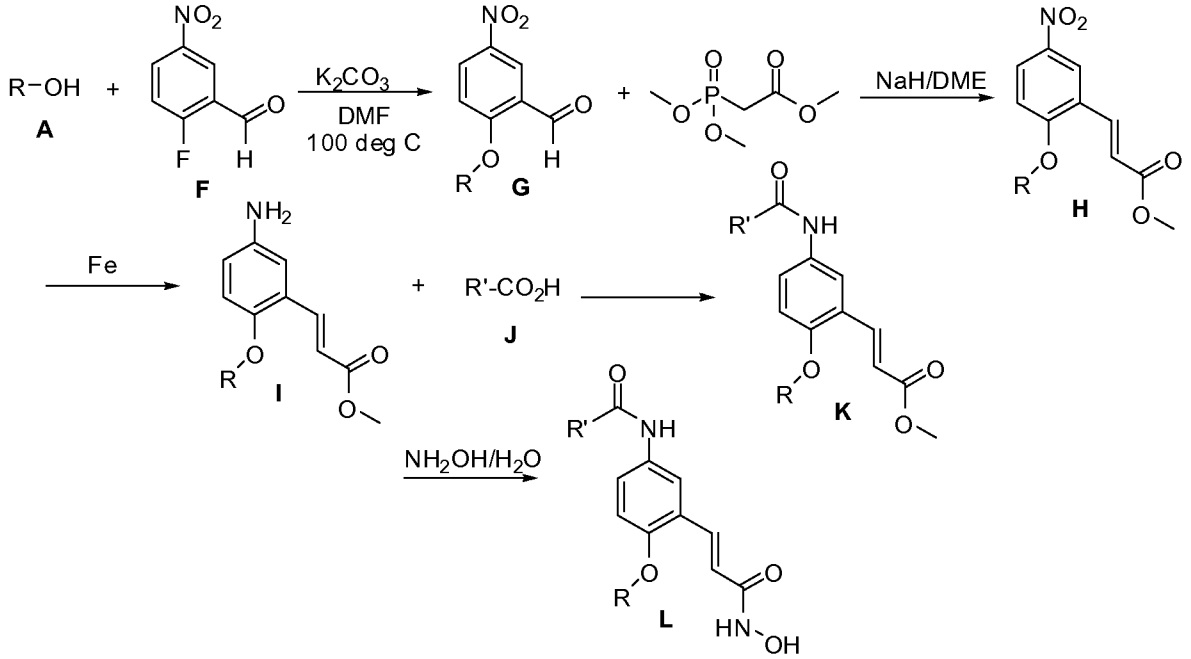
[00155] Cinnamic acid hydroxyamide compounds described herein are prepared from commercially available materials.

Synthetic Route I:



[00156] Cinnamic acid hydroxyamide compounds having the structure of compound **E** can be generally synthesized using Synthetic Route I shown above. Generally, alcohols of compound **A** (where R is for example, but not limited to, an aryl group, a heteroaryl group or C_2-C_{10}heterocycloalkyl group) are reacted with substituted benzaldehydes of compound **B** to form compounds having the structure **C**. Reaction of compounds **C** with trimethylphosphonoacetate results in compounds having the structure **D**. Reaction of compound **D** with a 50% solution of hydroxylamine results in compounds of structure **E**.

Synthetic Route II:



[00157] Cinnamic acid hydroxyamide compounds having the structure of compound **L** can be generally synthesized using Synthetic Route II shown above. Generally, alcohols of compound **A** (where R is for example, but not limited to, an aryl group, a heteroaryl group or C_2-C_{10}heterocycloalkyl group) are reacted with nitro substituted benzaldehydes of compound **F** to form compounds having the structure **G**. Reaction of compounds **G** with trimethylphosphonoacetate results in compounds having the structure **H**. Reduction of the nitro

group with Fe provides compounds of structure **I**. Reaction of carboxylic acid compounds **J** with compounds of structure **I** provides compounds of structure **K**. Reaction of compound **K** with a 50% solution of hydroxylamine results in compounds of structure **L**.

[00158] Throughout the specification, groups and substituents thereof are chosen to provide stable moieties and compounds.

Certain Terminology

[00159] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[00160] Definition of standard chemistry terms are found in reference works, including Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH ED." Vols. A (2000) and B (2001), Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed. In addition, nucleic acid and amino acid sequences for HDAC8 are disclosed in, e.g., U.S. Patent No. 6,875,598. Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Reactions and purification techniques are performed e.g., using kits of manufacturer's specifications or as described herein. The foregoing techniques and procedures are generally performed by conventional methods and as described in various general and more specific references that are cited and discussed throughout the present specification.

[00161] It is to be understood that the methods and compositions described herein are not limited to the particular methodology, protocols, cell lines, constructs, and reagents described herein and as such vary. It is also to be understood that the terminology used herein is for the

purpose of describing particular embodiments only, and is not intended to limit the scope of the methods, compounds, compositions described herein.

[00162] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . . C_1-C_x. C_1-C_x refers to the number of carbon atoms that make up the moiety to which it designates (excluding optional substitutents).

[00163] An "alkyl" group refers to an aliphatic hydrocarbon group. In some embodiments, the alkyl moiety is a "saturated alkyl" group, which means that it does not contain any alkene or alkyne moieties. In other embodiments, the alkyl moiety is an "unsaturated alkyl" moiety, which means that it contains at least one alkene or alkyne moiety. An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, is branched, straight chain, or cyclic.

[00164] The "alkyl" moiety has 1 to 10 carbon atoms (whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the alkyl group consists of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group of the compounds described herein are designated as "C_1-C_6 alkyl" or similar designations. By way of example only, "C_1-C_6 alkyl" indicates that there are one to six carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl, iso-pentyl, neo-pentyl, and hexyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. In some embodiments alkyl groups are substituted or unsubstituted. Depending on the structure, an alkyl group is either a monoradical or a diradical (i.e., an alkylene group).

[00165] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, buytloxy, cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

[00166] "Hydroxyalkyl" refers to an alkyl group substituted with hydroxy group(s).

[00167] "Hydroxyalkoxy" refers to an alkoxy substituted with hydroxy group(s).

[00168] "Hydroxyalkylaminoalkoxy" refers to an alkoxy substituted with an amino group with the amino group substituted with a hydroxyalkyl group as defined herein.

[00169] "Alkoxyalkyl" refers to alkyl group substituted with alkoxy group(s).

[00170] "Alkoxyalkyloxy" refers to an alkoxy group as defined herein substituted with alkoxy group as defined herein.

[00171] "Alkoxycarbonyl" refers to a -C(=O)O-(alkyl) group, where alkyl as defined herein. Non-limiting examples of alkoxycarbonyl groups include, e.g., methoxycarbonyl, ethoxycarbonyl, and the like.

[00172] "Alkoxycarbonylamino" refers to a –NR(C=O)-O-(alkyl), where alkyl is as defined herein and R is H, alkyl, heteroalkyl, haloalkyl, and the like.

[00173] The term "alkenyl" refers to a type of alkyl group in which the first two atoms of the alkyl group form a double bond that is not part of an aromatic group. That is, an alkenyl group begins with the atoms $–C(R)=CR_2$, wherein R refers to the remaining portions of the alkenyl group, which are the same or different. Non-limiting examples of an alkenyl group include $–CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CHCH_3$ and $–C(CH_3)=CHCH_3$. The alkenyl moiety is branched, straight chain, or cyclic (in which case, it would also be known as a "cycloalkenyl" group). Alkenyl groups have 2 to 6 carbons. In some embodiments alkenyl groups are substituted or unsubstituted. Depending on the structure, an alkenyl group is either a monoradical or a diradical (i.e., an alkenylene group).

[00174] "Alkenylcarbonyl" refers to a -C(O)-(alkenyl) group, where alkenyl is as defined herein.

[00175] "Alkenylcarbonyloxy" refers to a -OC(O)-(alkenyl) group, where alkenyl is as defined herein.

[00176] "Alkenyloxy" refers to a –O-(alkenyl) group, where alkenyl is as defined herein.

[00177] The term "alkynyl" refers to a type of alkyl group in which the first two atoms of the alkyl group form a triple bond. That is, an alkynyl group begins with the atoms –C≡C-R, wherein R refers to the remaining portions of the alkynyl group. Non-limiting examples of an alkynyl group include $–C≡CH$, $-C≡CCH_3$, $–C≡CCH_2CH_3$ and $–C≡CCH_2CH_2CH_3$. The "R" portion of the alkynyl moiety is branched, straight chain, or cyclic. In some embodiments an alkynyl group has 2 to 6 carbons. In other embodiments, alkynyl groups are substituted or unsubstituted. Depending on the structure, an alkynyl group is either a monoradical or a diradical (i.e., an alkynylene group).

[00178] "Amino" or "amine" refers to a $-NH_2$ group, an *N*-oxide derivative, an aliphatic amine or an aromatic amine. Aliphatic amines include: primary amines wherein one of hydrogen atoms is replaced by an organic substituent; secondary amines wherein two of hydrogen atoms are replaced by two organic substituents; and tertiary amines wherein all three substituents on the N atom are organic substituents.

[00179] The term "alkylamine" or "alkylamino" refers to the $-N(alkyl)_xH_y$ group, where alkyl is as defined herein and x and y are selected from the group x=1, y=1 and x=2, y=0. When x=2, the alkyl groups, taken together with the nitrogen to which they are attached, optionally form a cyclic ring system. The term "alkylamine" also refers to an amino group substituted with an alkyl group. "Dialkylamino" refers to a $-N(alkyl)_2$ group, where alkyl is as defined herein.

[00180] "Aminoalkyl" refers to an alkyl group as is defined herein that is substituted with an amino group.

[00181] "Aminoalkoxy" refers to an alkoxy group substitued with an amino group.

[00182] "Aminocarbonyl" refers to a $-CONH_2$ group.

[00183] "Aminosulfonyl" means an $-S(O)_2NH_2$ radical.

[00184] The term "alkylaminoalkyl" refers to an alkyl group, as is defined herein, substituted with an alkylamine as is defined herein. "Dialkylaminoalkyl" refers to an alkyl group that is substituted with a dialkylamino group.

[00185] "Alkylaminoalkoxy" refers to a alkoxy substituted with an alkylamine.

[00186] "Alkylaminocarbonyl" means a -C(O)R radical where R is alkylamino as defined herein.

[00187] "Alkylaminocarbonylamino" refers to –NHC(=O)-(alkylamino).

[00188] "Alkylaminocarbonyloxy" refers to –OC(=O)-(alkylamino).

[00189] "Alkylaminosulfonyl" refers to $-S(=O)_2NHR$ radical where R is alkyl, as defined herein.

[00190] "Alkylcarbonyl" means a -C(=O)R radical where R is alkyl as defined herein.

[00191] "Alkylcarbonylamino" means a -NR'C(=O)-(alkyl), where R' is hydrogen, alkyl, haloalkyl, heteroalkyl.

[00192] "Alkylcarbonyloxy" means a -OC(=O)R radical where R is alkyl as defined herein.

[00193] "Dialkylaminoalkyloxy" refers to a alkoxy susbtituted with a dialkylamino.

[00194] "Dialkylaminocarbonyl" refers to -C(=O)R, where R is dialkylamino.

[00195] "Dialkylaminocarbonylamino" refers to –NR'-C(=O)-(dialkylamino), where R' is hydrogen, alkyl, heteroalkyl, haloalkyl, and dialkylaminocarbonyl as defined herein.

[00196] "Dialkylaminocarbonyloxy" means an –O(C=O)-(dialkylamino), dialkylaminocarbonyl as defined herein.

[00197] "Dialkylaminosulfonyl" refers to $-S(O)_2NR_2$, where R is alkyl as defined herein.

[00198] As used herein, the term "ring" refers to any covalently closed structure. Rings include, for example, carbocycles (e.g., aryls and cycloalkyls), heterocycles (e.g., heteroaryls and non-aromatic heterocycles), aromatics (e.g. aryls and heteroaryls), and non-aromatics (e.g.,

cycloalkyls and non-aromatic heterocycles). In some embodiments, rings are optionally substituted. In other embodiments rings are monocyclic or polycyclic.

[00199] The term "membered ring" refers to any cyclic structure. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, for example, cyclohexyl, phenyl, pyridine, piperidine, morpholine, piperazine, pyridazine, pyrimidine, pyrazine, pyran and thiopyran are 6-membered rings; and cyclopentyl, pyrrolidine, imidazole, oxazole, thiazole, pyrrole, furan, and thiophene are 5-membered rings.

[00200] The term "carbocyclic" or "carbocycle" refers to a ring wherein each of the atoms forming the ring is a carbon atom. Carbocycle includes aryl and cycloalkyl. The term thus distinguishes carbocycle from heterocycle ("heterocyclic") in which the ring backbone contains at least one atom which is different from carbon (i.e a heteroatom). Heterocycle includes heteroaryl and heterocycloalkyl. In some embodiments carbocycles and heterocycles are optionally substituted.

[00201] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. In some embodiments aromatic rings are formed from five, six, seven, eight, nine, or more than nine atoms. In other embodiments aromatics are optionally substituted. The term "aromatic" includes both carbocyclic aryl ("aryl", *e.g.*, phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

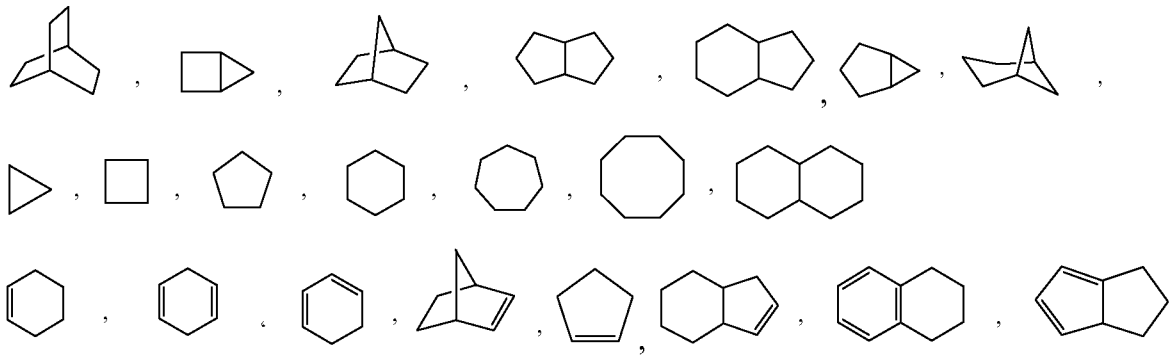
[00202] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. In some embodiments, aryl rings are formed by five, six, seven, eight, nine, ten or more than ten carbon atoms. In some embodiments, aryl groups are optionally substituted. In some embodiments, an aryl is a C_6-C_{10}aryl. Examples of aryl groups include, but are not limited to phenyl, and naphthalenyl. In one aspect, an aryl is a phenyl. Depending on the structure, an aryl group is either a monoradical or a diradical (i.e., an arylene group).

[00203] "Aralkyl" or "arylalkyl" refers to an alkyl group as is defined herein substituted with an aryl group as is defined herein.

[00204] "Phenylalkyl" refers to an alkyl substituted with a phenyl.

[00205] The term "cycloalkyl" refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyls are saturated, or partially unsaturated. In some embodiments. cycloalkyls are fused with an aromatic

ring. Cycloalkyl groups include groups having from 3 to 10 ring atoms. Illustrative examples of cycloalkyl groups include, but are not limited to, the following:



, and the like. Cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In one aspect, a cycloalkyl is a C_3-C_6cycloalkyl.

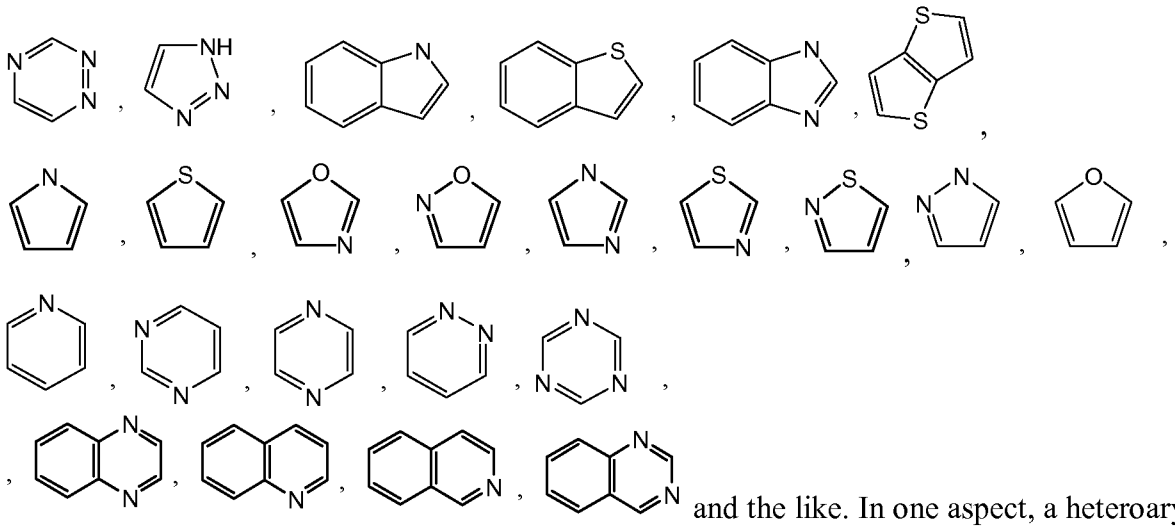
[00206] "Cycloalkylalkyl" refers to an alkyl, as is defined herein, substituted with a cycloalkyl, as is defined herein.

[00207] "Cycloalkylcarbonyl" refers to -C(=O)-cycloalkyl.

[00208] The term "heterocycle" refers to heteroaromatic and heteroalicyclic groups containing one to four ring heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups include groups having 3 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 3-membered heterocyclic group is aziridinyl (derived from aziridine). An example of a 4-membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5-membered heterocyclic group is thiazolyl. An example of a 6-membered heterocyclic group is pyridyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl,

triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups are C-attached or *N*-attached where such is possible. For example, a group derived from pyrrole is named pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole is named imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one.

[00209] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. An *N*-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. Polycyclic heteroaryl groups are fused or non-fused. Illustrative examples of heteroaryl groups include the following moieties:



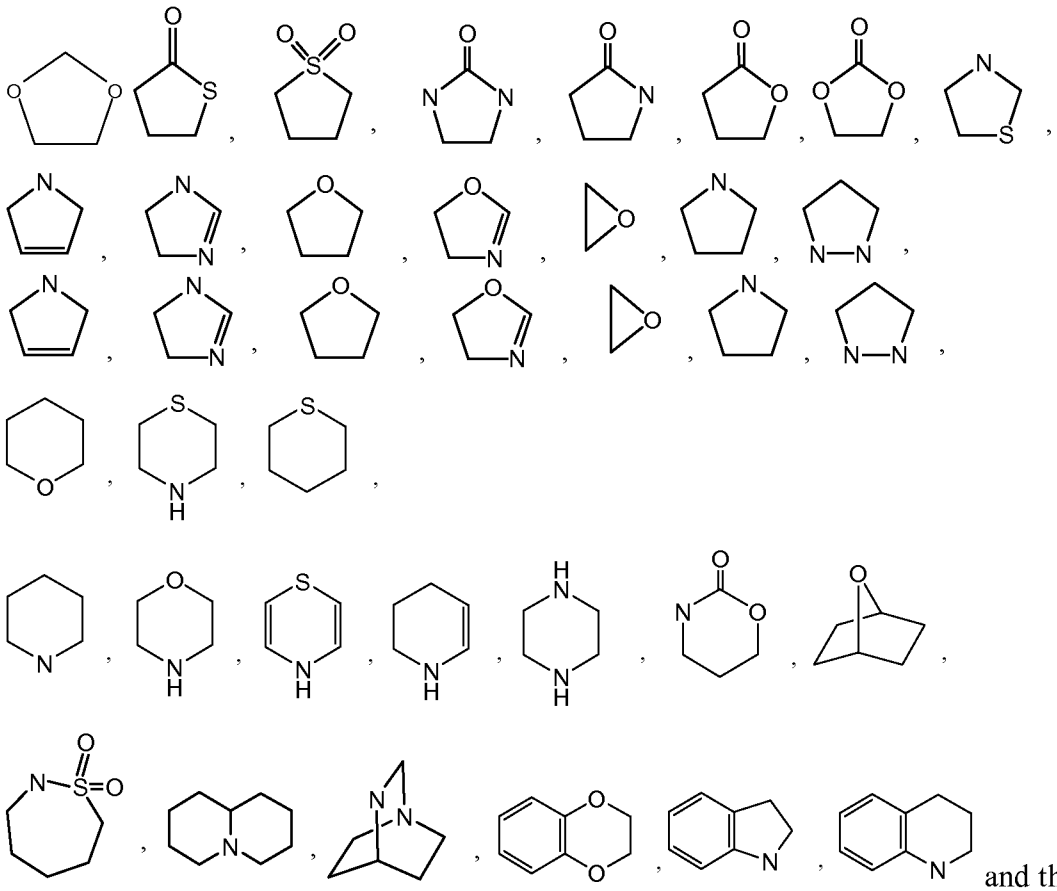
and the like. In one aspect, a heteroaryl includes 0-3 N atoms. In one aspect, a heteroaryl includes 1-3 N atoms. In one aspect, a heteroaryl includes 0-3 N atoms, 0-1 O atoms, and 0-1 S atoms. In one aspect, a heteroaryl is a monocyclic or bicyclic heteroaryl. In one aspect, a heteroaryl is a monocyclic heteroaryl. In one aspect, the heteroaryl is a C_1-C_{10}heteroaryl. In another aspect, the heteroaryl is a C_2-C_9heteroaryl. In one aspect, monocyclic heteroaryl is a C_1-C_5heteroaryl. In one aspect, bicyclic heteroaryl is a C_5-C_{10}heteroaryl. Depending on the structure, a heteroaryl group can be a monoradical or a diradical (i.e., a heteroarylene group).

[00210] In some embodiments, substituted or unsubstituted heteroaryl groups are selected from among pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, 4-azaindolyl, 5-azaindolyl, 6-azaindolyl, 7-azaindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl,

oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl. In other embodiments, substituted or unsubstituted heteroaryl groups are selected from among pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl. In yet other embodiments, substituted or unsubstituted heteroaryl groups are selected from among pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl, pyridazinyl, quinazolinyl, quinoxalinyl. In still other embodiments, substituted or unsubstituted heteroaryl groups are selected from among pyridinyl, and quinolinyl.

[00211] "Heteroaralkyl" or "heteroarylalkyl" refers to an alkyl, as is defined herein, substituted with a heteroaryl as is defined herein.

[00212] A "heteroalicyclic" group or "heterocycloalkyl" group refers to a cycloalkyl group, wherein at least one skeletal ring atom is a heteroatom selected from nitrogen, oxygen and sulfur. The radicals are fused with an aryl or heteroaryl. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:



and the like. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to

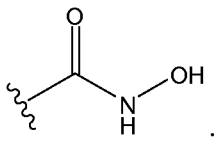
the monosaccharides, the disaccharides and the oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteratoms) that make up the heterocycloalkyl (i.e skeletal atoms of the heterocycloalkyl ring). In one aspect, a heterocycloalkyl is a C_2-C_{10}heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_4-C_{10}heterocycloalkyl.

[00213] In some embodiments, substituted or unsubstituted heterocycloalkyl groups are selected from among quinolizinyl, dioxinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiazinyl, tetrahydropyridinyl, piperazinyl, oxazinanonyl, dihydropyrrolyl, dihydroimidazolyl, tetrahydrofuranyl, tetrahydropyranyl, dihydrooxazolyl, oxiranyl, pyrrolidinyl, pyrazolidinyl, dihydrothienyl, imidazolidinonyl, pyrrolidinonyl, dihydrofuranonyl, dioxolanonyl, thiazolidinyl, piperidinonyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and tetrahydrothienyl. In other embodiments, substituted or unsubstituted heterocycloalkyl groups are selected from among piperidinyl, morpholinyl, piperazinyl, dihydropyrrolyl, dihydroimidazolyl, tetrahydrofuranyl, dihydrooxazolyl, pyrrolidinyl, pyrazolidinyl, dihydrothienyl, imidazolidinonyl, pyrrolidinonyl, piperidinonyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and tetrahydrothienyl. In yet other embodiments, substituted or unsubstituted heterocycloalkyl groups are selected from among piperidinyl, morpholinyl, piperazinyl, tetrahydrofuranyl, pyrrolidinyl, pyrrolidinonyl, piperidinonyl, indolinyl, tetrahydroquinolinyl, and tetrahydrothienyl. In some embodiments, substituted or unsubstituted heterocycloalkyl groups are selected from among piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and pyrrolidinyl.

[00214] "Heterocycloalkylalkyl" refers to an alkyl, as defined herein, substituted with a heterocycloalkyl, as defined herein.

[00215] "Heterocycloalkylalkoxy" refers to an alkoxy, as defined herein, substituted with a heterocycloalkyl, as defined herein wherein heterocycloalkyl includes alkyl substituents.

[00216] The term "hydroxamate", "hydroxamic acid", "N-hydroxycarboxamide" or "carboxylic acid hydroxyamide" refers to:



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[00217] The term "halo" or, alternatively, "halogen" means fluoro, chloro, bromo and iodo.

[00218] The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halogens. In some embodiments, the halogens are the same or are different. The terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine. Non-limiting examples of haloalkyls include $-CH_2Cl$, $-CF_3$, $-CHF_2$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF(CH_3)_3$, and the like. Non-limiting examples of fluoroalkyls include $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CF(CH_3)_3$, and the like. Non-limiting examples of haloalkoxy groups include $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CF_3$, $-OCF_2CF_3$, $-OCF_2CF_2CF_3$, $-OCF(CH_3)_3$, and the like.

[00219] The terms "heteroalkyl" "heteroalkenyl" and "heteroalkynyl" include optionally substituted alkyl, alkenyl and alkynyl radicals and which have one or more skeletal chain atoms selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus, silicon, or combinations thereof. The heteroatom(s) are placed at any position of the heteroalkyl group. In some embodiments, up to two heteroatoms are consecutive, such as, by way of example, $-CH_2$-NH-OCH_3 and $-CH_2$-O-$Si(CH_3)_3$. Excluding the number of heteroatoms, a "heteroalkyl" includes from 1 to 6 carbon atoms, a "heteroalkenyl" includes from 2 to 6 carbons atoms, and a "heteroalkynyl" includes from 2 to 6 carbon atoms.

[00220] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00221] "Cyanoalkylaminocarbonyl" refers to a $-C(=O)NR'$(cyanoalkyl) group, where R' is hydrogen, alkyl, heteroalkyl, haloalkyl, as is defined herein, cyanoalkyl is as defined herein.

[00222] An "isothiocyanato" group refers to a -NCS group.

[00223] "Alkylthio" means an -SR radical where R is alkyl as defined herein.

[00224] "Acylamino" refers to a $RC(=O)N(R')$- group, where R' is hydrogen, hydroxy, alkyl, or alkoxy. In some embodiments, R' is H or R.

[00225] "Alkylsulfinyl" means an -S(O)R radical where R is alkyl as defined herein.

[00226] "Alkylsulfonyl" means a $-SO_2R$ radical where R is alkyl as defined herein.

[00227] "Alkylsulfonylamino" means a $-N(R')SO_2R$ group, where R' is hydrogen, alkyl, heteroalkyl, haloalkyl, as is defined herein, and R is alkyl as is defined herein.

[00228] "Phenylsulfonyl" refers to means a $-S(=O)_2$-phenyl moiety.

[00229] "Phenylsulfonylamino" refers to a $-NR'SO_2$-(phenyl) where R' is hydrogen, alkyl, heteroalkyl, haloalkyl, as is defined herein.

[00230] "Heteroarylaminocarbonyl" refers to a -C(=O)NR'(heteroaryl) group, where R' is hydrogen, alkyl, heteroalkyl, haloalkyl, as is defined herein, and heteroaryl is as defined herein.

[00231] "Arylaminocarbonyl" refers to a -C(=O)NR'(aryl) group, where R' is hydrogen, alkyl, heteroalkyl, haloalkyl, as is defined herein, and aryl is as defined herein.

[00232] "Arylcarbonylamino" refers to -NR'C(=O)-(aryl) group, where R' is hydrogen, alkyl, heteroalkyl, haloalkyl, as is defined herein, and aryl is as defined herein.

[00233] As used herein, the substituent "R" appearing by itself and without a number designation refers to a substituent selected from among from alkyl, haloalkyl, heteroalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, heterocycloalkyl, and heterocycloalkylalkyl.

[00234] The term "optionally substituted" or "substituted" means that the referenced group is substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, acyl, acyloxy, isocyanato, thiocyanato, isothiocyanato, nitro, haloalkyl, fluoroalkyl, and amino, including mono- and di-substituted amino groups (e.g. $-NH_2$, -NHR, $-N(R)_2$), and the protected derivatives thereof. By way of example, an optional substituent is L^sR^s, wherein each L^s is independently selected from a bond, -O-, -C(=O)-, -S-, -S(=O)-, $-S(=O)_2-$, -NH-, -NHC(O)-, -C(O)NH-, $S(=O)_2NH-$, $-NHS(=O)_2$, -OC(O)NH-, -NHC(O)O-, $-(C_1-C_6alkyl)-$, or $-(C_2-C_6alkenyl)-$; and each R^s is independently selected from among H, (C_1-C_6alkyl), (C_3-C_8cycloalkyl), aryl, heteroaryl, heteocycloalkyl, and C_1-C_6heteroalkyl. In one aspect, substituted groups are substituted with one or more substituents selected from halogen, -OH, $-OC_1-C_4$alkyl, C_1-C_4alkyl, C_1-C_4heteroalkyl, C_1-C_4fluoroalkyl and $-OC_1-C_4$fluoroalkyl. In yet other aspect, substituted groups are substituted with one or more substituents selected from F, Cl, Br, -OH, $-OCH_3$, $-CH_3$, and $-CF_3$. In yet other embodiments, substituted groups are substituted with one or more substituents selected from F, Cl, and Br. In one aspect, substituted groups are substituted with one of the preceding groups. The protecting groups that form the protective derivatives of the above substituents are found in references such as Greene and Wuts, above.

[00235] The compounds presented herein possess one or more stereocenters and each center exists in the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers are obtained, if desired, by separation of stereoisomers by chiral chromatographic columns.

[00236] The methods and formulations described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds having

the structure of Formula I, as well as active metabolites of these compounds having the same type of activity. In some situations, compounds exist as tautomers. All tautomers are included within the scope of the compounds presented herein. In addition, the compounds described herein exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00237] The terms "kit" and "article of manufacture" are used as synonyms.

[00238] The term "subject" or "patient" encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

[00239] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

[00240] A "selective HDAC8 inhibitor," as used herein, refers to a compound that has an IC_{50} for inhibition of HDAC8 deacetylase activity that is at least about 5 fold to more than about 500 fold lower than the IC_{50} for inhibition of deacetylase activity of another HDAC. In some embodiments, the selective HDAC8 inhibitor has an IC_{50} for inhibition of HDAC8 deacetylase activity that is about 5, about 10, about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450 or more than about 500 fold lower than the IC_{50} for inhibition of deacetylase activity of another HDAC. In one embodiment, the selective HDAC8 inhibitor has an IC_{50} for inhibition of HDAC8 deacetylase activity that is at least about 10 fold lower than the IC_{50} for inhibition of deacetylase activity of at least one of HDAC1, HDAC2, HDAC3, HDAC6, HDAC10, and HDAC11; in another embodiment at least two of HDAC1, HDAC2, HDAC3, HDAC6, HDAC10, and HDAC11; in another embodiment all of HDAC1, HDAC2, HDAC3, HDAC6, HDAC10, and HDAC11. In another embodiment, the selective HDAC8 inhibitor has an IC_{50} for HDAC8 deacetylase activity that is at least about 20 fold lower than the IC_{50} for inhibition of deacetylase activity of at least one of HDAC1, HDAC2, HDAC3,

HDAC6, HDAC10, and HDAC11; in another embodiment at least two of HDAC1, HDAC2, HDAC3, HDAC6, HDAC10, and HDAC11; in another embodiment all of HDAC1, HDAC2, HDAC3, HDAC6, HDAC10, and HDAC11.

[00241] As used herein, amelioration of the symptoms of a particular disease, disorder or condition by administration of a particular compound or pharmaceutical composition refers to any lessening of severity, delay in onset, slowing of progression, or shortening of duration, whether permanent or temporary, lasting or transient that is attributed to or associated with administration of the compound or composition.

[00242] The terms "inhibits", "inhibiting", or "inhibitor" of HDAC, as used herein, refer to inhibition of histone deacetylase activity.

[00243] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00244] By "pharmaceutically acceptable," as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material is administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00245] The term "pharmaceutical composition" refers to a mixture of the compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound include but are not limited to: intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration.

[00246] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result is reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a HDAC8 inhibiting compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is determined using techniques, such as a dose escalation study.

[00247] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00248] The terms "co-administration" or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00249] The term "carrier," as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells or tissues.

[00250] The term "diluent" refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents are also used to stabilize compounds because they provide a more stable environment. Salts dissolved in buffered solutions (which also provide pH control or maintenance) are utilized, including, but not limited to a phosphate buffered saline solution.

[00251] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. Further information on metabolism is obtained from The Pharmacological Basis of Therapeutics, 9th Edition, McGraw-Hill (1996). Metabolites of the compounds disclosed herein are identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds.

[00252] "Bioavailability" refers to the percentage of the weight of compounds disclosed herein, that is delivered into the general circulation of the animal or human being studied. The total exposure (AUC(0-∞)) of a drug when administered intravenously is usually defined as 100% bioavailable (F%). "Oral bioavailability" refers to the extent to which the compounds disclosed

herein, are absorbed into the general circulation when the pharmaceutical composition is taken orally as compared to intravenous injection.

[00253] "Plasma concentration" refers to the concentration of the compounds disclosed herein, in the plasma component of blood of a subject. It is understood that the plasma concentration of the compounds described herein vary significantly between subjects, due to variability with respect to metabolism and/or possible interactions with other therapeutic agents. In accordance with one embodiment disclosed herein, the blood plasma concentration of the compounds disclosed herein vary from subject to subject. Likewise, values such as maximum plasma concentration (Cmax) or time to reach maximum plasma concentration (Tmax), or total area under the plasma concentration time curve (AUC(0-∞)) varies from subject to subject. Due to this variability, the amount necessary to constitute "a therapeutically effective amount" of a compound varies from subject to subject.

[00254] "Pharmacokinetics" refers to the factors which determine the attainment and maintenance of the appropriate concentration of drug at a site of action.

Examples of Pharmaceutical Compositions and Methods of Administration

[00255] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, intramuscular injection, subcutaneous injection, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[00256] The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00257] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner. In other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

[00258] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are

formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Fo*rms *and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

[00259] A pharmaceutical composition refers to a mixture of a HDAC8 inhibitor compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to a mammal.

[00260] In one embodiment, HDAC8 inhibitor compounds described herein are formulated in an aqueous solution. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, HDAC8 inhibitor compounds described herein are formulated for transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated. In still other embodiments wherein the compounds described herein are formulated for other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions.

[00261] In another embodiment, compounds described herein are formulated for oral administration. The compounds described herein are formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

[00262] In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or pills. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium

carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00263] Oral dosage forms also include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules contain one or more active compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

[00264] In still other embodiments, the HDAC8 inhibitor compounds described herein are administered topically. Topically administrable compositions include solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments.

[00265] In other embodiments, the HDAC8 inhibitor compounds described herein are formulated for administration by inhalation. Various forms suitable for administration by inhalation include, but are not limited to, aerosols, mists or powders.

[00266] The active ingredient in the pharmaceutical compositions is in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. All tautomers of the compounds described herein are included within the scope of the compounds presented herein. Additionally, the compounds described herein encompass unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

[00267] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease

or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial.

[00268] In prophylactic applications, compositions comprising the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. In this use, the precise amounts also depend on the patient's state of health, weight, and the like.

[00269] In some embodiments pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the active compounds into preparations which are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

Examples of Methods of Dosing and Treatment Regimens

[00270] The compounds described herein are used in the preparation of medicaments for the inhibition of HDAC8, or for the treatment of diseases or conditions that would benefit, at least in part, from inhibition of HDAC8. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing at least one compound described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

[00271] The compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. Amounts effective for this use will depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. One determines such therapeutically effective amounts by, e.g., a dose escalation clinical trial).

[00272] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. One determines such prophylactically effective amounts by e.g., a dose escalation clinical trial. When

used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

[00273] In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00274] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the compounds are given continuously; alternatively, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). The length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. In some embodiments, the dose reduction during a drug holiday is from about 10% to about 100%, including, by way of example only, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

[00275] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. Some patients require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00276] The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease or condition and its severity, the identity (e.g., weight) of the subject or host in need of treatment, but will be determined according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. In general, however, doses employed for adult human treatment will typically be in the range of about 0.02 to about 5000 mg per day, in other embodiments about 1 to about 1500 mg per day. In some embodiments the desired dose is presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00277] The pharmaceutical composition described herein is in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. The unit dosage is in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. Aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection are presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative.

[00278] The daily dosages appropriate for the compounds described herein described herein are from about 0.01 to about 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, including, but not limited to, humans, is in the range from about 0.5 mg to about 100 mg, conveniently administered in divided doses, including, but not limited to, up to four times a day or in extended release form. Suitable unit dosage forms for oral administration include from about 1 to about 50 mg active ingredient. The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. Such dosages are altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00279] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD50 and ED50. Compounds exhibiting high therapeutic indices are contemplated herein. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for use in human. In some embodiments, the dosage of such compounds lies within a range of circulating concentrations that include the ED50 with minimal toxicity. The dosage varies within this range depending upon the dosage form employed and the route of administration utilized.

Combination Treatments

[00280] The compounds and compositions described herein are also used in combination with other therapeutic agents that are selected for their therapeutic value for the condition to be

treated. In general, the compositions described herein and, in embodiments where combinational therapy is employed, other agents are not administered in the same pharmaceutical composition, and are administered by different routes because of different physical and chemical characteristics. The initial administration is made according to established protocols and based upon the observed effects, the dosage, modes of administration and times of administration.

[00281] In certain instances, it is appropriate to administer at least one compound described herein in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein, such as a hydroxamic acid compound described herein, is nausea, then it is appropriate to administer an anti-nausea agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein is enhanced by administration of an adjuvant (i.e., by itself the adjuvant has minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit experienced by a patient is increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient is additive of the two therapeutic agents or the patient experiences a synergistic benefit.

[00282] The particular choice of compounds used will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol. The compounds are administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the disease, disorder, or condition, the condition of the patient, and the actual choice of compounds used. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is determined after evaluation of the disease being treated and the condition of the patient.

[00283] For combination therapies described herein, dosages of the co-administered compounds will vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In addition, when co-administered with one or more biologically active agents, the compound provided herein is administered either simultaneously with the biologically active agent(s), or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein in combination with the biologically active agent(s).

[00284] In any case, the multiple therapeutic agents (one of which is a HDAC8 selective compound described herein) are administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents are provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). In some embodiments the therapeutic agents are given in multiple doses, or both are given as multiple doses. If not simultaneous, the timing between the multiple doses varies from more than zero weeks to less than four weeks. In addition, the combination methods, compositions and formulations are not to be limited to the use of only two agents; the use of multiple therapeutic combinations is also envisioned.

[00285] It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is modified in accordance with a variety of factors. These factors include the disorder or condition from which the subject suffers, as well as the age, weight, sex, diet, and medical condition of the subject. Thus, the dosage regimen actually employed varies widely and therefore deviates from the dosage regimens set forth herein.

[00286] The pharmaceutical agents which make up the combination therapy disclosed herein are a combined dosage form or in separate dosage forms intended for substantially simultaneous administration. The pharmaceutical agents that make up the combination therapy are administered sequentially, with either therapeutic compound being administered by a regimen calling for two-step administration. The two-step administration regimen calls for sequential administration of the active agents or spaced-apart administration of the separate active agents. The time period between the multiple administration steps ranges from, a few minutes to several hours, depending upon the properties of each pharmaceutical agent, such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the pharmaceutical agent. Circadian variation of the target molecule concentration also determines the optimal dose interval.

[00287] In addition, the compounds described herein are used in combination with procedures that provide additional or synergistic benefit to the patient. By way of example only, patients are expected to find therapeutic and/or prophylactic benefit in the methods described herein, wherein pharmaceutical composition of a compound disclosed herein and /or combinations with other therapeutics are combined with genetic testing to determine whether that individual is a carrier of a mutant gene that is known to be correlated with certain diseases or conditions.

[00288] The compounds described herein and combination therapies are administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound varies. Thus, for example, the compounds are used as a prophylactic and are administered continuously to subjects with a propensity to develop

conditions or diseases in order to prevent the occurrence of the disease or condition. The compounds and compositions are administered to a subject during or as soon as possible after the onset of the symptoms. The administration of the compounds are initiated within the first 48 hours of the onset of the symptoms, in other embodiments, within the first 48 hours of the onset of the symptoms, in further embodiments, within the first 6 hours of the onset of the symptoms, and in yet further embodiments within 3 hours of the onset of the symptoms. The initial administration is via any route practical, such as, for example, an intravenous injection, a bolus injection, infusion over 5 minutes to about 5 hours, a pill, a capsule, transdermal patch, buccal delivery, and the like, or combination thereof. In some embodiments, a compound is administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, for example, from about 1 month to about 3 months. The length of treatment varies for each subject, and the length is determined using the known criteria. For example, the compound or a formulation containing the compound is administered for at least 2 weeks, in some embodiments, about 1 month to about 5 years, and in other embodiments from about 1 month to about 3 years.

Anti-Cancer Agents

[00289] Combinations of selective HDAC8 inhibitors described herein with other anti-cancer or chemotherapeutic agents are described herein. Examples of such anti-cancer or chemotherapeutic agents are found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. Combinations of agents are determined based on the particular characteristics of the drugs and the cancer involved.

[00290] The term "combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. In some embodiments, the combination is a fixed combination. The term "fixed combination" means that the active ingredients, e.g. a cinnamic hydroxyamide compound described herein, and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. In some embodiments, the combination is a non-fixed combination. The term "non-fixed combination" means that the active ingredients, e.g. a compound described herein, and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[00291] In one aspect, HDAC inhibitors disclosed herein are administered in combination with an agent selected from anthrocyclins, fludarabine, flavopiridol, imatinib, bortezomib, anti-angiogenesis agents and nuclear receptor ligands, such as, all-trans retinoic acid and tumor necrosis factor-related apoptosis-inducing ligand.

[00292] Anti-cancer agents and/or agents used in chemotherapy include, but are not limited to, the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, nitrogen mustards, nitroso ureas, angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling pathway, apoptosis inducing agents, agents that interfere with cell cycle checkpoints, agents that interfere with receptor tyrosine kinases (RTKs), integrin blockers, NSAIDs, inhibitors of inherent multidrug resistance (MDR), anti-emetic agents, agents useful in the treatment of anemia, agents useful in the treatment of neutropenia, immunologic-enhancing drugs, biphosphonates, aromatase inhibitors, agents inducing terminal differencation of neoplastic cells, γ-secretase inhibitors, cancer vaccines, and any combination thereof.

[00293] Where the subject is suffering from a cancer (e.g., a T-cell lymphoma), a selective HDAC8 inhibitor is used in any combination with one or more other anti-cancer agents. Examples of anti-cancer agents include, but are not limited to, any of the following: 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib, 17-N-allylamino-17-demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, or PD184352.

[00294] Taxol™, also referred to as "paclitaxel", which is a well-known anti-cancer drug which acts by enhancing and stabilizing microtubule formation, and analogs of Taxol™, such as Taxotere™. Compounds that have the basic taxane skeleton as a common structure feature, have also been shown to have the ability to arrest cells in the G2-M phases due to stabilized microtubules and are useful for treating cancer in combination with the compounds described herein.

[00295] Other anti-cancer agents that are employed in combination with a selective HDAC8 inhibitor include Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin;

cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin Il (including recombinant interleukin II, or rlL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-l a; interferon gamma-l b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride.

[00296] Other anti-cancer agents that are employed in combination with a selective HDAC8 inhibitor include: 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-

dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin

A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1 -based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine;

thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

[00297] Yet other anticancer agents that are employed in combination with a selective HDAC8 inhibitor include alkylating agents, antimetabolites, natural products, or hormones, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, etc.), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, ete.), or triazenes (decarbazine, etc.). Examples of antimetabolites include but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin).

[00298] Examples of natural products useful in combination with a selective HDAC8 inhibitor include but are not limited to vinca alkaloids (e.g., vinblastin, vincristine), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), or biological response modifiers (e.g., interferon alpha).

[00299] Examples of alkylating agents that are employed in combination a selective HDAC8 inhibitor include, but are not limited to, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan, etc.), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin, etc.), or triazenes (decarbazine, ete.). Examples of antimetabolites include, but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin.

[00300] Examples of hormones and antagonists useful in combination with a selective HDAC8 inhibitor include, but are not limited to, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), gonadotropin releasing hormone analog (e.g., leuprolide, SPD-424).

[00301] In another embodiment, Dynepo gene activated erythropoietin (Anti-anemic; human erythropoietin) is admistered in combination with selective HDAC8 inhibitor compounds.

[00302] "Estrogen receptor modulators" refers to compounds that interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpr-opanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646. In some embodiments, estrogen receptor modulators are tamoxifen and raloxifene.

[00303] "Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

[00304] "Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-*cis*-retinoic acid, 9-*cis*-retinoic acid, α-difluoromethylornithine, ILX23-7553, *trans*-*N*-(4'-hydroxyphenyl)retinamide, and N-4-carboxyphenyl retinamide.

[00305] Other agents that are used in the methods and compositions described herein for the treatment or prevention of cancer include platinum coordination complexes (e.g., cisplatin, carboblatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide).

[00306] Examples of anti-cancer agents which act by arresting cells in the G2-M phases due to stabilized microtubules and which are used in combination with a selective HDAC8 inhibitor include without limitation the following marketed drugs and drugs in development: Erbulozole (also known as R-55104), Dolastatin 10 (also known as DLS-10 and NSC-376128), Mivobulin isethionate (also known as CI-980), Vincristine, NSC-639829, Discodermolide (also known as NVP-XX-A-296), ABT-751 (Abbott, also known as E-7010), Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (also known as LU-103793 and NSC-D-669356), Epothilones (such as Epothilone A, Epothilone B, Epothilone C (also known as desoxyepothilone A or dEpoA), Epothilone D (also referred to as KOS-862, dEpoB, and desoxyepothilone B), Epothilone E,

Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (also known as BMS-310705), 21-hydroxyepothilone D (also known as Desoxyepothilone F and dEpoF), 26-fluoroepothilone), Auristatin PE (also known as NSC-654663), Soblidotin (also known as TZT-1027), LS-4559-P (Pharmacia, also known as LS-4577), LS-4578 (Pharmacia, also known as LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, also known as WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, also known as ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (also known as LY-355703), AC-7739 (Ajinomoto, also known as AVE-8063A and CS-39.HCI), AC-7700 (Ajinomoto, also known as AVE-8062, AVE-8062A, CS-39-L-Ser.HCI, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (also known as NSC-106969), T-138067 (Tularik, also known as T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, also known as DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (also known as BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, also known as SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, lnanocine (also known as NSC-698666), 3-lAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, also known as T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, lsoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (also known as NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, also known as D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (also known as SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi).

[00307] "Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere

with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of histone deacetylase, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

[00308] Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, *cis*-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (*trans, trans, trans*)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine-(chloro)platinum(II)]-tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

[00309] Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-*N*-(3-fluoro-4-methoxyphenyl)-benzene sulfonamide, anhydrovinblastine, *N,N*-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS188797.

[00310] Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-*N,N*-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H)propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)-ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, *N*-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a,5aB,8aa,9b)-9-[2-[*N*-[2-(dimethylamino)ethyl]-*N*-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)colchic(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-

hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)-amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, *N*-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, *N*-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2-, 1-c]quinolin-7-one, and dimesna.

[00311] "Antiproliferative agents" include antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxy- cytidine, *N*-[5-(2,3-dihydro-benzofuryl)sulfonyl]-*N'*-(3,4-dichlorophenyl)urea, *N*6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]-glycylamino]-L-glycero-B-L-manno-heptopyranosyl]-adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetra cyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. "Antiproliferative agents" also includes monoclonal antibodies to growth factors, other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes, such as p53, which are delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example).

[00312] "Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (±)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, (-)-6-[amino(4-chloropheny- l)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethyl- phenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, (*S*)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)-methyl)-2-piperazinone, 5(S)-n-butyl-1-(2-

methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[*N*-(1-(4-cyanobenzyl)-1H-imidazol-5-yl- ethyl)carbamoyl]-piperidine, 4-{5-[4-hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 18,19-dihydro-19-oxo-5H,17H-6,10:12,16-dimetheno-1H-imidazo[4,3-c][1,11,4]dioxa-azacyclononadecine-9-carbonitrile, (±)-19,20-dihydro-19-oxo-5H-18,21-ethano-12,14-etheno-6,10-metheno-22H-benzo[d]imidazo[4,3-k][1,6,9,12]-oxatriaza-cyclooctadecine-9-carbonitrile, 19,20-dihydro-19-oxo-5H,17H-18,21-ethano-6,10: 12,16-dimetheno-22H-imidazo[3,4-h][1,8,11,14]oxatriazacyclo-eicosine-9-carbonitrile, and (±)-19,20-dihydro-3-methyl-19-oxo-5H-18,21-ethano-12,14-etheno-6,10-metheno-22H-benzo[d]imidazo[4,3-k][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile.

[00313] For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *J. Of Cancer*, Vol. 35, No. 9, pp.1394-1401 (1999).

[00314] Examples of HIV protease inhibitors include amprenavir, abacavir, CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir, saquinavir, ABT-378, AG 1776, and BMS-232, 632. Examples of reverse transcriptase inhibitors include delaviridine, efavirenz, GS-840, HB Y097, lamivudine, nevirapine, AZT, 3TC, ddC, and ddI. It has been reported (*Nat. Med.*;8(3):225-32, 2002) that HIV protease inhibitors, such as indinavir or saquinavir, have potent anti-angiogenic activities and promote regression of Kaposi sarcoma.

[00315] "Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR20), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib, valecoxib, and rofecoxib, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et at., *J. Lab. Clin. Med.* 105:

141-145 (1985)), and antibodies to VEGF (see, *Nature Biotechnology*, Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature*, 362, 841-844 (1993); WO 00/44777; and WO 00/61186).

[00316] Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]-methyl]-1H-1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RP14610, NX31838, sulfated mannopentose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonyl-imino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

[00317] "Inhibitors of cell proliferation and survival signaling pathway" refer to pharmaceutical agents that inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR, inhibitors of CD20 (rituximab), inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PDK (for example LY294002), serine/threonine kinases, inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI- 1040 and PD-098059) and inhibitors of mTOR (for example Wyeth CCI-779 and Ariad AP23573). Such agents include small molecule inhibitor compounds and antibody antagonists.

[00318] "Apoptosis inducing agents" include, but not limited to, activators of TNF receptor family members (including the TRAIL receptors).

[00319] "Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chkl and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

[00320] "Agents that interfere with receptor tyrosine kinases (RTKs)" refer to compounds that inhibit RTKs and therefore mechanisms involved in oncogenesis and tumor progression. Such agents include, but not limited to, tyrosine kinase inhibitors such as inhibitors of c-Kit, Eph, PDGF, Flt3, Lck, Btk, and c-Met. Further agents include inhibitors of RTKs shown as described by Bume-Jensen and Hunter, 2001, *Nature* 411: 355-365. Examples of "tyrosine kinase inhibitors" include, but not limited to, *N*-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]-quinazoline, *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-

quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, ST1571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7- H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, SU11248, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

[00321] HDAC inhibitors are also useful in combination with platelet fibrinogen receptor (GP Iib/IIIa) antagonists, such as tirofiban, to inhibit metastasis of cancerous cells. Tumor cells activate platelets largely via thrombin generation. This activation is associated with the release of VEGF. The release of VEGF enhances metastasis by increasing extravasation at points of adhesion to vascular endothelium (Amirkhosravi, 1999, *Platelets* 10: 285-292). Therefore, HDAC inhibitors serve to inhibit metastasis, in combination with GP Iib/IIIa) antagonists. Examples of other fibrinogen receptor antagonists include abciximab, eptifibatide, sibrafiban, lamifiban, lotrafiban, cromofiban, and CT50352.

[00322] As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counter-act binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$; $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

[00323] Commercially available anti-cancer agents which are used in combination with an HDAC8 selective agent disclosed herein include, but are not limited to: abarelix (Plenaxis®); aldesleukin (Prokine®); Aldesleukin (Proleukin®); Alemtuzumab (Campath®); alitretinoin (Panretin®); allopurinol (Zyloprim®); altretamine (Hexalen®); amifostine (Ethyol®); anastrozole (Arimidex®); arsenic trioxide (Trisenox®); asparaginase (Elspar®); azacitidine (Vidaza®); bevacizumab (Avastin®); bexarotene (Targretin®); bleomycin (Blenoxane®); bortezomib (Velcade®); busulfan (Busulfex®); busulfan (Myleran®); calusterone (Methosarb®); capecitabine Xeloda®); carboplatin Paraplatin®); carmustine (BCNU, BiCNU); carmustine (Gliadel®); celecoxib (Celebrex®); cetuximab (Erbitux®); chlorambucil (Leukeran®); cisplatin (Platinol®); cladribine (Leustatin®); clofarabine (Clolar®); cyclophosphamide (Cytoxan®); cytarabine (Cytosar-U®); cytarabine liposomal (DepoCyt); dacarbazine (DTIC-Dome);

dactinomycin(actinomycin D, Cosmegen®); Darbepoetin alfa (Aranesp®); dasatinib (Sprycel®); daunorubicin liposomal (DanuoXome); daunorubicin (daunomycin, Daunorubicin®); daunorubicin(daunomycin, Cerubidine®); decitabine (Dacogen®); denileukin (Ontak®); dexrazoxane (Zinecard®); docetaxel (Taxotere®); doxorubicin (Adriamycin®); doxorubicin liposomal (Doxil®); dromostanolone propionate; epirubicin (Ellence®); Epirubicin; Epoetin alfa (EPOGEN®); erlotinib (Tarceva®); estramustine (Emcyt®); etoposide phosphate (Etopophos®); etoposide (VP-16; Vepesid®); exemestane (AROMASIN®); fentanyl citrate (Fentora®); Filgrastim (Neupogen®); floxuridine (FUDR); fludarabine (Fludara®); fluorouracil (5-FU, Adrucil®); fulvestrant (Faslodex®); gefitinib (Iressa®); gemcitabine (Gemzar®); gemtuzumab ozogamicin (Mylotarg®); goserelin acetate (Zoladex®); histrelin acetate (Histrelin®); hydroxyurea (Hydrea®); Ibritumomab Tiuxetan (Zevalin®); idarubicin (Idamycin®); ifosfamide (IFEX®); imatinib mesylate (Gleevec®); interferon alfa 2a (Roferon A®); Interferon alfa-2b (Intron A®); irinotecan (Camptosar®); lenalidomide (Revlimid®); letrozole (Femara®); leucovorin (Leucovorin®); Leuprolide Acetate (Eligard®); levamisole (Ergamisol®); lomustine, CCNU CeeBU®); meclorethamine(nitrogen mustard, Mustargen®); megestrol acetate (Megace®); melphalan (Alkeran®); mercaptopurine (6-MP, Purinethol®); mesna (Mesnex®); methotrexate (Rheumatrex®, Trexall®); methoxsalen (Uvadex®); mitomycin C (Mutamycin®); mitomycin C (Mitozytrex®); mitotane (Lysodren®); mitoxantrone (Novantrone®); nandrolone phenpropionate (Durabolin-50); nelarabine (Arranon®); Nofetumomab (Verluma®); Oprelvekin (Neumega®); oxaliplatin (Eloxatin®); paclitaxel (Paxene®); paclitaxel (Taxol®); paclitaxel protein-bound particles (Abraxane®); palifermin (Kepivance®); pamidronate (Aredia®); panitumumab (Vectibix®); pegademase (Adagen®); pegaspargase (Oncaspar®); Pegfilgrastim (Neulasta®); pemetrexed disodium (Alimta®); pentostatin (Nipent®); pipobroman (Vercyte®); plicamycin, mithramycin (Mithracin®); porfimer sodium (Photofrin®); procarbazine (Matulane®); quinacrine (Atabrine®); Rasburicase (Elitek®); rituximab (Rituxan®); sargramostim (Leukine®); Sargramostim (Prokine®); sorafenib (Nexavar®); streptozocin (Zanosar®); sunitinib maleate (Sutent®); talc (Sclerosol®); tamoxifen (Nolvadex®); temozolomide (Temodar®); teniposide (VM-26, Vumon®); testolactone (Teslac®); thalidomide (Thalomid®); thioguanine (6-TG, Thioguanine®); thiotepa (Thioplex®); topotecan (Hycamtin®); toremifene (Fareston®); Tositumomab (Bexxar®); Tositumomab/I-131 tositumomab (Bexxar®); trastuzumab (Herceptin®); tretinoin (ATRA, Vesanoid®); Uracil Mustard; valrubicin (Valstar®); vinblastine (Velban®); vincristine (Oncovin®); vinorelbine (Navelbine®); vorinostat (Zolinza®); zoledronate (Zometa®); and zoledronic acid (Zometa®).

[00324] In some embodiments, the HDAC8 selective compounds described herein are used in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall *et al.* (*Am J Hum Genet* 61:785-789, 1997) and Kufe *et al.* (*Cancer Medicine*, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy is used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which are delivered via recombinant virus-mediated gene transfer, Duc- 4, NF-I, NF-2, RB, WTl, BRCAl, BRCA2, a uPA/uPAR antagonist ("Adenoviras-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," *Gene Therapy*, August 1998, 5(8): 1105-13), and interferon-γ (*J. Immunol.* 2000; 164:217- 222).

[00325] In other embodiments, the HDAC8 selective compounds described herein are administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

[00326] In some embodiments, the HDAC8 selective compounds described herein are employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which result from the use of a HDAC8 selective compound described herein, alone or with radiation therapy. For the prevention or treatment of emesis, a HDAC8 selective compound described herein is used in conjunction with anti-emetic agents, such as, but not limited to: neurokinin-1 receptor antagonists, 5HT3 receptor antagonists (such as ondansetron, granisetron, tropisetron, Palonosetron, and zatisetron), $GABA_B$ receptor agonists (such as baclofen), corticosteroids (such as dexamethasone, prednisone, prednisolone, dopamine antagonists (such as, but not limited to, domperidone, droperidol, haloperidol, chlorpromazine, promethazine, prochlorperazine, metoclopramide), antihistamines (H1 histamine receptor antagonists, such as but not limited to, cyclizine, diphenhydramine, dimenhydrinate, meclizine, promethazine, hydroxyzine), cannabinoids (such as but not limited to, cannabis, marinol, dronabinol), and others (such as, but not limited to, trimethobenzamide; ginger, emetrol, propofol).

[00327] In one embodiment, an anti-emesis agent selected from among a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is administered as an adjuvant for the treatment or prevention of emesis that results upon administration of the instant compounds.

[00328] In other embodiments, the HDAC8 selective compounds described herein are administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin-α).

[00329] In other embodiments, the HDAC8 selective compounds described herein are administered with an agent useful in the treatment of neutropenia. Examples of agents useful in the treatment of neutropenia include, but are not limited to, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

[00330] In some embodiments, the HDAC8 selective compounds described herein are administered with an immunologic-enhancing drug, such as levamisole, bacillus Calmette-Guerin, octreotide, isoprinosine and Zadaxin.

[00331] In other embodiments, the HDAC8 selective compounds described herein are useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel®), pamidronate (Aredia®), alendronate (Fosamax®), risedronate(Actonel®), zoledronate (Zometa®), ibandronate (Boniva®), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

[00332] In other embodiments, the HDAC8 selective compounds described herein are useful for treating breast cancer in combination with aromatase inhibitors. Examples of aromatase inhibitors include but are not limited to: anastrozole, letrozole and exemestane.

[00333] In some embodiments, the HDAC8 selective compounds described herein are useful for treating or preventing cancer in combination with siRNA or RNAi therapeutics.

[00334] "DNA methyltransferase inhibitor" refers to compounds which inhibit the methylation of the DNA base cytosine at the C-5 position of that base by the DNA methyltransferase enzyme. In some embodiments, DNA methyltransferase inhibitors include 5-azacytosine and zebularine®.

Radiation therapy

[00335] Radiotherapy, also called radiation therapy, is the treatment of cancer and other diseases with ionizing radiation. Ionizing radiation deposits energy that injures or destroys cells in an area being treated (a "target tissue") by damaging their genetic material, making it impossible for these cells to continue to grow. Although radiation damages both cancer cells and normal cells, the latter are better able to repair themselves and function properly. Radiotherapy is used to treat localized solid tumors, such as cancers of the skin, tongue, larynx, brain, breast, prostate, colon, uterus and/or cervix. It is also used to treat leukemia and lymphoma (cancers of the blood-forming cells and lymphatic system, respectively).

[00336] A technique for delivering radiation to cancer cells is to place radioactive implants directly in a tumor or body cavity. This is called internal radiotherapy (brachytherapy, interstitial irradiation, and intracavitary irradiation are types of internal radiotherapy.) Using internal radiotherapy, the radiation dose is concentrated in a small area, and the patient stays in the hospital for a few days. Internal radiotherapy is frequently used for cancers of the tongue, uterus, prostate, colon, and cervix.

[00337] The term "radiotherapy" or "ionizing radiation" include all forms of radiation, including but not limited to α, β, and γ radiation and ultra violet light. Radiotherapy with or without concurrent or sequential chemotherapy is an effective modality for head and neck, breast, skin, anogenital cancers, and certain nonmalignant diseases such as keloid, desmoid tumor, hemangioma, arteriovenous malformation, and histocytosis X.

[00338] Provided are methods of using at least one histone deacetylase inhibitor to reduce side effect caused by at least one other therapeutic treatment, such as radiation-induced normal tissue fibrosis or chemotherapy-induced tissue necrosis, and the methods provided herein also synergistically inhibit tumor cell growth with radiotherapy and other anti-cancer agents.

Growth Hormone Secretagogues

[00339] In some embodiments, a selective inhibitor of HDAC8 is used in combination with one or more growth hormone secretagogues including, but not limited to, arginine, L-3,4-dihydroxyphenylalanine (1-Dopa), glucagon, vasopressin, PACAP (pituitary adenylyl cyclase activating peptide), muscarinic receptor agonists and a synthethic hexapeptide, GHRP (growth hormone releasing peptide).

Agents for Treating Autoimmune Diseases, Inflammatory Diseases, or Allergy Diseases

[00340] In one embodiment, where the subject is suffering from or at risk of suffering from an autoimmune disease, an inflammatory disease, or an allergy disease, a selective HDAC8 inhibitor compound is administered in any combination with one or more of the following therapeutic agents: immunosuppressants (e.g., tacrolimus, cyclosporin, rapamicin, methotrexate , cyclophosphamide, azathioprine, mercaptopurine, mycophenolate, or FTY720), glucocorticoids (e.g., prednisone, cortisone acetate, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, fludrocortisone acetate, deoxycorticosterone acetate, aldosterone), non-steroidal anti-inflammatory drugs (e.g., salicylates, arylalkanoic acids, 2-arylpropionic acids, N-arylanthranilic acids, oxicams, coxibs, or sulphonanilides), Cox-2-specific inhibitors (e.g., valdecoxib, celecoxib, or rofecoxib), leflunomide, gold thioglucose, gold thiomalate, aurofin, sulfasalazine, hydroxychloroquinine, minocycline, TNF-α binding proteins (e.g., infliximab, etanercept, or adalimumab), abatacept, anakinra, interferon-β, interferon-γ,

interleukin-2, allergy vaccines, antihistamines, antileukotrienes, beta-agonists, theophylline, or anticholinergics.

[00341] In one embodiment, selective HDAC8 inhibitor compounds described herein, or compositions and medicaments that include the selective HDAC8 inhibitor compounds described herein, are administered to a patient in combination with an anti-inflammatory agent including, but not limited to, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (glucocorticoids).

[00342] NSAIDs include, but are not limited to: aspirin, salicylic acid, gentisic acid, choline magnesium salicylate, choline salicylate, choline magnesium salicylate, choline salicylate, magnesium salicylate, sodium salicylate, diflunisal, carprofen, fenoprofen, fenoprofen calcium, flurobiprofen, ibuprofen, ketoprofen, nabutone, ketolorac, ketorolac tromethamine, naproxen, oxaprozin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, meclofenamate, meclofenamate sodium, mefenamic acid, piroxicam, meloxicam, COX-2 specific inhibitors (such as, but not limited to, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337 and NS398).

[00343] Combinations with NSAIDs, which are selective COX-2 inhibitors, are contemplated herein.

[00344] Compounds that have been described as selective COX-2 inhibitors and are therefore useful in the methods or pharmaceutical compositions describede herein include, but are not limited to, celecoxib, rofecoxib, lumiracoxib, etoricoxib, valdecoxib, and parecoxib, or a pharmaceutically acceptable salt thereof.

[00345] Corticosteroids, include, but are not limited to: betamethasone, prednisone, alclometasone, aldosterone, amcinonide, beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, clobetasone, clocortolone, cloprednol, cortisone, cortivazol, deflazacort, deoxycorticosterone, desonide, desoximetasone, desoxycortone, dexamethasone, diflorasone, diflucortolone, difluprednate, fluclorolone, fludrocortisone, fludroxycortide, flumetasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin, fluocortolone, fluorometholone, fluperolone, fluprednidene, fluticasone, formocortal, halcinonide, halometasone, hydrocortisone/cortisol, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone butyrate, loteprednol, medrysone, meprednisone, methylprednisolone, methylprednisolone aceponate, mometasone furoate, paramethasone, prednicarbate, prednisone/prednisolone, rimexolone, tixocortol, triamcinolone, and ulobetasol.

[00346] In one embodiment, HDAC8 selective inhibitors are administered in combination with leukotriene receptor antagonists including, but are not limited to, BAY u9773, Cuthbert *et al* EP

00791576 (published 27 Aug 1997), DUO-LT (Tsuji *et al*, *Org. Biomol. Chem.*, 1, 3139-3141, 2003), zafirlukast (Accolate®), montelukast (Singulair®), prankulast (Onon®), and derivatives or analogs thereof.

Kits/Articles of Manufacture

[00347] For use in the therapeutic applications described herein, kits and articles of manufacture are also described herein. Such kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) including one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers are formed from a variety of materials such as glass or plastic.

[00348] The articles of manufacture provided herein contain packaging materials. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any disease, disorder, or condition that would benefit by inhibition of HDAC activity, or in which HDAC is a mediator or contributor to the symptoms or cause.

[00349] For example, the container(s) include one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example a container that is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[00350] A kit will include one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also be included.

[00351] A label is attached on or associated with the container. A label is attached on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label is used to

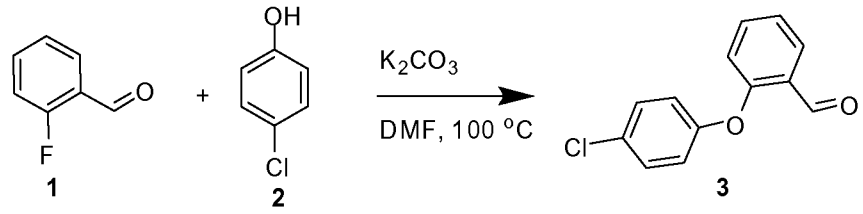
indicate that the contents are to be used for a specific therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein.

[00352] In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack, for example, contains metal or plastic foil, such as a blister pack. The pack or dispenser device is accompanied by instructions for administration. The pack or dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

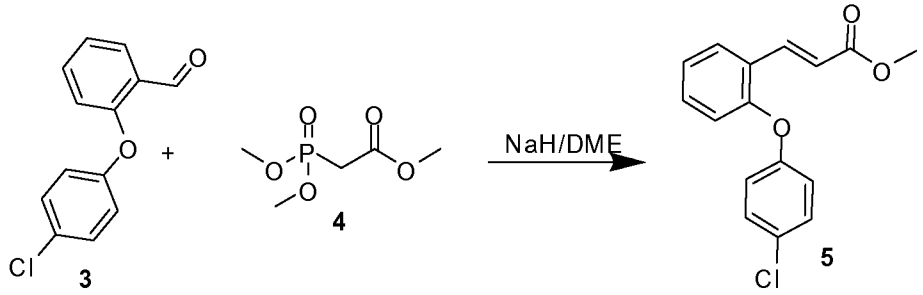
EXAMPLES

[00353] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein. The starting materials and reagents used for the synthesis of the compounds described herein are synthesized or obtained from commercial sources, such as, Sigma-Aldrich, Fluka, Acros Organics, Alfa Aesar, Bachem and the like.

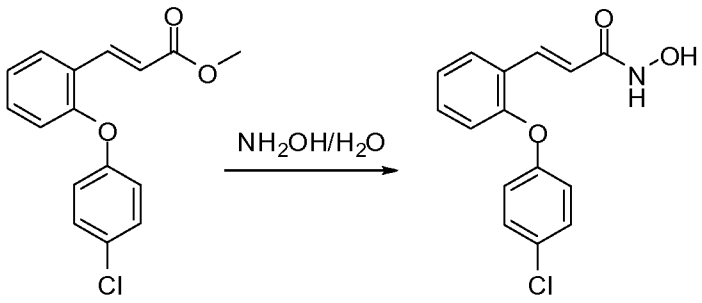
Example 1: Synthesis of (*E*)-3-(2-(4-chlorophenoxy)phenyl)-*N*-hydroxyacrylamide (6)



[00354] Step 1: A mixture of 2-fluoro-benzaldehyde (**1**, 7.0g, 56.4 mmol), 4-chlorophenol (**2**, 7.25 g, 56.4 mmol) and K_2CO_3 (12.0 g, 85 mmol) in 50 mL DMF was heated overnight at 100 °C. Progress of the reaction was monitored by LC/MS. After reaction completion, the reaction mixture was cooled, poured into water (30 mL) and then extracted twice with EtOAc. The EtOAc layers were combined and washed with water, then brine and dried with $MgSO_4$. After filtration and concentration, the crude material was purified by flash chromatography (hexane/EtOAc: 0-100%) to provide 9.0 g (69% yield) of 2-(4-chlorophenoxy)benzaldehyde (**3**).



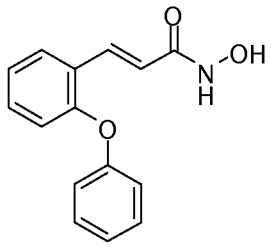
[00355] Step 2: To a solution of 2-(4-chlorophenoxy)benzaldehyde (**3**, 0.5 g, 2.15 mmol) and trimethyl phosphonoacetate (**4**, 0.47 g, 2.6 mmol) in 20 mL of DMF was added NaH (95%) (62 mg, 2.6 mmol). The mixture was stirred overnight at 100 °C. The DME was evaporated, then water was added to quench the reaction and extracted twice with EtOAc. The EtOAc layers were combined, washed with water, then brine and dried with $MgSO_4$. After filtration and concentration, 0.57 g (90% yield: >90% purity by UV254) of (*E*)-methyl 3-(2-(4-chlorophenoxy)phenyl)acrylate (**5**) was isolated and used without further purification.



5 6

[00356] Step 3: To a cooled solution of (*E*)-methyl 3-(2-(4-chlorophenoxy)phenyl)acrylate (**5**, 0.29 g, 1.0 mmol) in IPA (5 mL) was added 50% NH_2OH/H_2O (1.0 g, 30 mmol), and then 1N NaOH (2 mmol, 2 mL). The reaction mixture was stirred for 1 hr at 0 °C, then acidified to pH = 7, diluted with water, and then extrated with EtOAc (3X50 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. After filtration and evaporation, 0.24 g (84% yield) of (*E*)-3-(2-(4-chlorophenoxy)phenyl)-*N*-hydroxyacrylamide (**6**) was isolated. The crude material was purified by HPLC. EM (calc): 289.05; MS (M+1H) = 290.0.

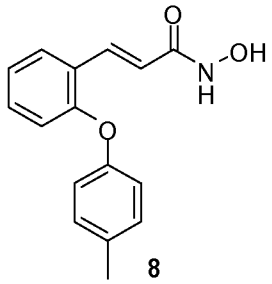
Example 2: Synthesis of (*E*)-*N*-Hydroxy-3-(2-phenoxyphenyl)acrylamide (7)



7

[00357] The title compound was synthesized as described in Example 1. EM (calc): 255.09; MS (M+1H) = 256.5.

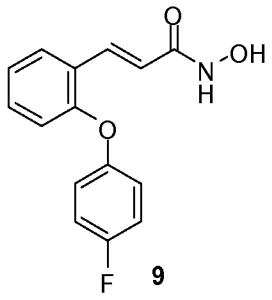
Example 3: Synthesis of (*E*)-3-(2-(*p*-Tolyloxy)phenyl)-*N*-hydroxyacrylamide (8)



8

[00358] The title compound was synthesized as described in Example 1. EM (calc): 269.11; MS (M+1H) = 270.5.

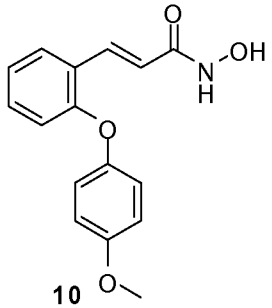
Example 4: Synthesis of (*E*)-3-(2-(4-Fluorophenoxy)phenyl)-*N*-hydroxyacrylamide (9)



9

[00359] The title compound was synthesized as described in Example 1. EM (calc): 273.08; MS (M+1H) = 274.0.

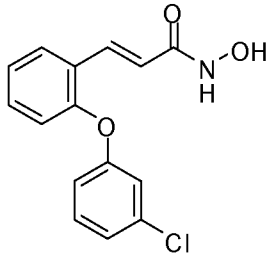
Example 5: Synthesis of (*E*)-N-hydroxy-3-(2-(4-methoxyphenoxy)phenyl)acrylamide (10)



10

[00360] The title compound was synthesized as described in Example 1. EM (calc): 285.1; MS (M+1H) = 286.0.

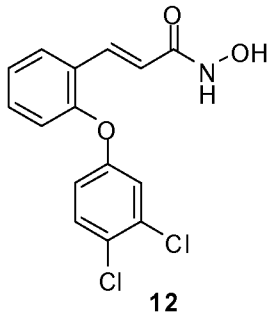
Example 6: Synthesis of (*E*)-3-(2-(3-Chlorophenoxy)phenyl)-*N*-hydroxyacrylamide (11)



11

[00361] The title compound was synthesized as described in Example 1. EM (calc): 289.05; MS (M+1H) = 290.0.

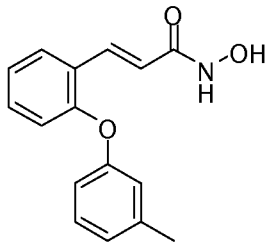
Example 7: Synthesis of (*E*)-3-(2-(3,4-Dichlorophenoxy)phenyl)-*N*-hydroxyacrylamide (12)



12

[00362] The title compound was synthesized as described in Example 1. EM (calc): 323.01; MS (M+1H) = 324.5.

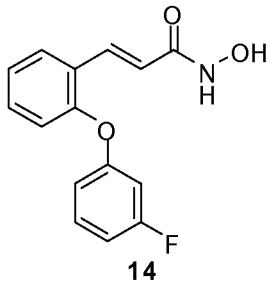
Example 8: Synthesis of (*E*)-N-hydroxy-3-(2-(m-tolyloxy)phenyl)acrylamide (13)



13

[00363] The title compound was synthesized as described in Example 1. EM (calc): 269.11; MS (M+1H) = 270.5.

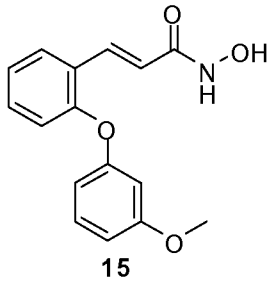
Example 9: Synthesis of (*E*)-3-(2-(3-Fluorophenoxy)phenyl)-*N*-hydroxyacrylamide (14)



14

[00364] The title compound was synthesized as described in Example 1. EM (calc): 273.08; MS (M+1H) = 274.0.

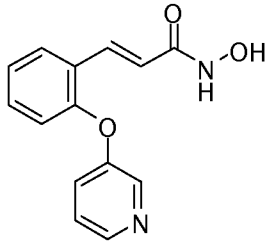
Example 10: Synthesis of (*E*)-N-hydroxy-3-(2-(3-methoxyphenoxy)phenyl)acrylamide (15)



15

[00365] The title compound was synthesized as described in Example 1. EM (calc): 285.1; MS (M+1H) = 286.5.

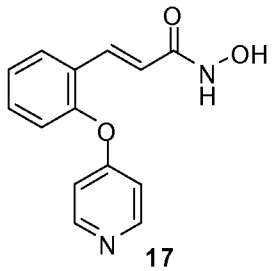
Example 11: (*E*)-*N*-Hydroxy-3-(2-(pyridin-3-yloxy)phenyl)acrylamide (16)



16

[00366] The title compound was synthesized as described in Example 1. EM (calc): 256.08; MS (M+1H) = 257.5.

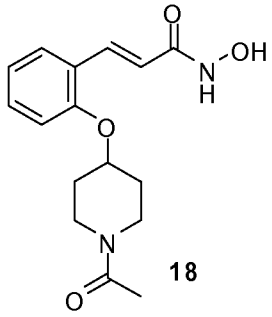
Example 12: Synthesis of (*E*)-*N*-Hydroxy-3-(2-(pyridin-4-yloxy)phenyl)acrylamide (17)



17

[00367] The title compound was synthesized as described in Example 1. EM (calc): 256.08; MS (M+1H) = 257.5.

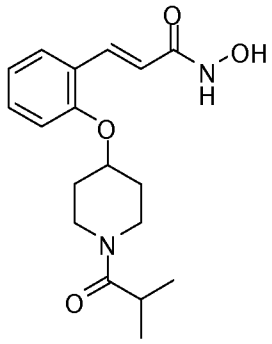
Example 13: Synthesis of (*E*)-3-(2-(1-acetylpiperidin-4-yloxy)phenyl)-N-hydroxyacrylamide (18)



18

[00368] The title compound was synthesized as described in Example 1. EM (calc): 304.14; MS (M+1H) = 305.5.

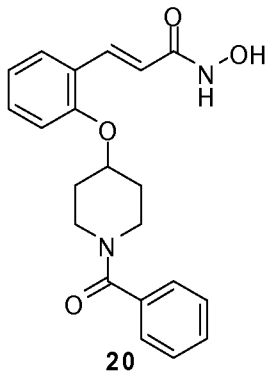
Example 14: Synthesis of (*E*)-N-hydroxy-3-(2-(1-isobutyrylpiperidin-4-yloxy)phenyl)acrylamide (19)



19

[00369] The title compound was synthesized as described in Example 1. EM (calc): 332.17; MS (M+1H) = 333.5.

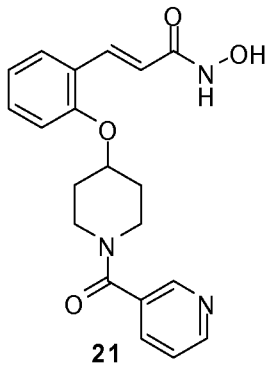
Example 15: Synthesis of (E)-3-(2-(1-benzoylpiperidin-4-yloxy)phenyl)-N-hydroxyacrylamide (20)



20

[00370] The title compound was synthesized as described in Example 1. EM (calc): 366.16; MS (M+1H) = 367.0.

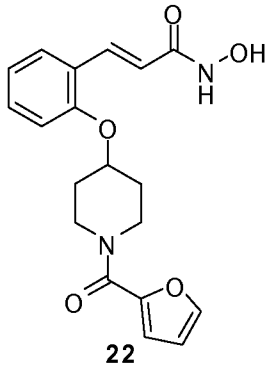
Example 16: Synthesis of (*E*)-N-hydroxy-3-(2-(1-nicotinoylpiperidin-4-yloxy)phenyl)acrylamide (21)



21

[00371] The title compound was synthesized as described in Example 1. EM (calc): 367.15; MS (M+1H) = 368.0.

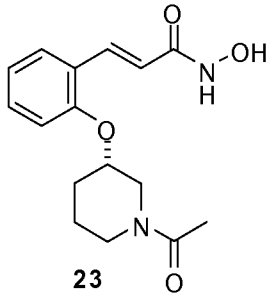
Example 17: Synthesis of (*E*)-3-(2-(1-(furan-2-carbonyl)piperidin-4-yloxy)phenyl)-N-hydroxyacrylamide (22)



22

[00372] The title compound was synthesized as described in Example 1. EM (calc): 356.14; MS (M+1H) = 357.0.

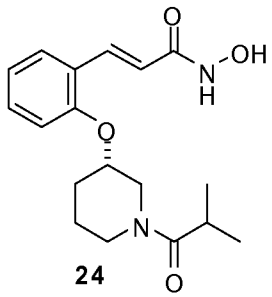
Example 18: Synthesis of (S,E)-3-(2-(1-acetylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide (23)



23

[00373] The title compound was synthesized as described in Example 1. EM (calc): 304.14; MS (M+1H) = 305.5.

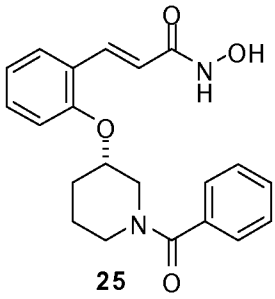
Example 19: Synthesis of (S,E)-N-hydroxy-3-(2-(1-isobutyrylpiperidin-3-yloxy)phenyl)acrylamide (24)



24

[00374] The title compound was synthesized as described in Example 1. EM (calc): 332.17; MS (M+1H) = 333.5.

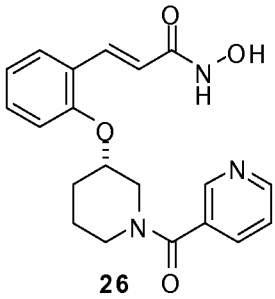
Example 20: Synthesis of (S,E)-3-(2-(1-benzoylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide (R,E)-3-(2-(1-benzoylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide (25)



25

[00375] The title compound was synthesized as described in Example 1. EM (calc): 366.16; MS (M+1H) = 367.0.

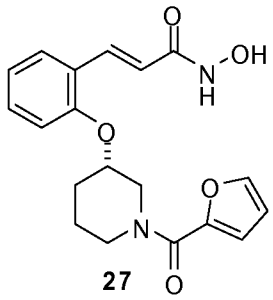
Example 21: Synthesis of (S,E)-N-hydroxy-3-(2-(1-nicotinoylpiperidin-3-yloxy)phenyl)acrylamide (26)



26

[00376] The title compound was synthesized as described in Example 1. EM (calc): 367.15; MS (M+1H) = 368.5.

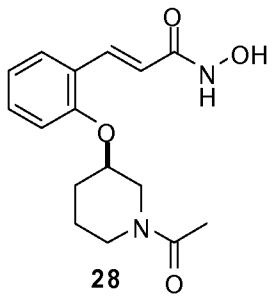
Example 22: Synthesis of (S,E)-3-(2-(1-(furan-2-carbonyl)piperidin-3-yloxy)phenyl)-N-hydroxyacrylamide (27)



27

[00377] The title compound was synthesized as described in Example 1. EM (calc): 356.14; MS (M+1H) = 357.5.

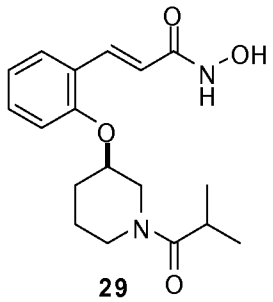
Example 23: Synthesis of (R,E)-3-(2-(1-acetylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide (28)



28

[00378] The title compound was synthesized as described in Example 1. EM (calc): 304.14; MS (M+1H) = 305.5.

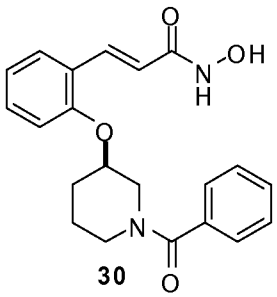
Example 24: Synthesis of (R,E)-N-hydroxy-3-(2-(1-isobutyrylpiperidin-3-yloxy)phenyl)acrylamide (29)



29

[00379] The title compound was synthesized as described in Example 1. EM (calc): 332.17; MS (M+1H) = 333.5.

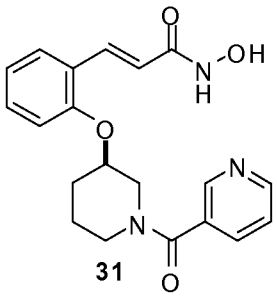
Example 25: Synthesis of (R,E)-3-(2-(1-benzoylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide (30)



30

[00380] The title compound was synthesized as described in Example 1. EM (calc): 366.16; MS (M+1H) = 367.0.

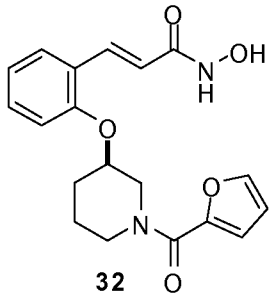
Example 26: Synthesis of (R,E)-N-hydroxy-3-(2-(1-nicotinoylpiperidin-3-yloxy)phenyl)acrylamide (31)



31

[00381] The title compound was synthesized as described in Example 1. EM (calc): 367.15; MS (M+1H) = 368.0.

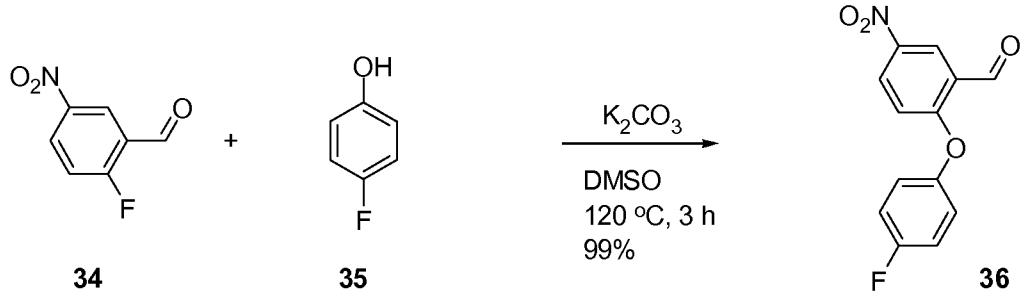
Example 27: Synthesis of (R,E)-3-(2-(1-(furan-2-carbonyl)piperidin-3-yloxy)phenyl)-N-hydroxyacrylamide (32)



32

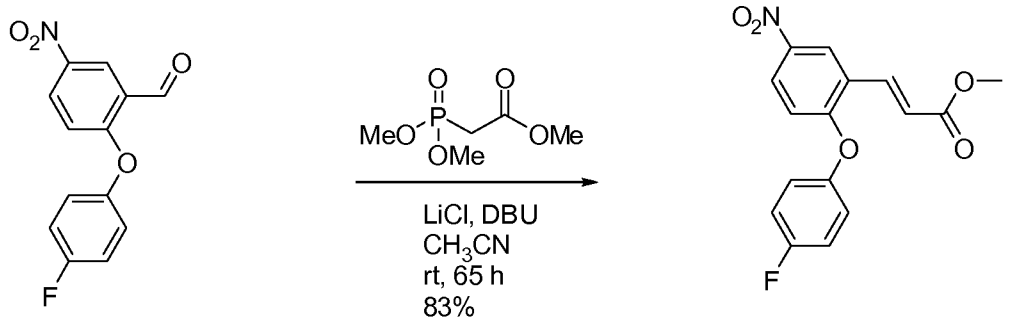
[00382] The title compound was synthesized as described in Example 1. EM (calc): 356.14; MS (M+1H) = 357.5.

Example 28: Synthesis of (E)-N-(4-(4-fluorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide (33)



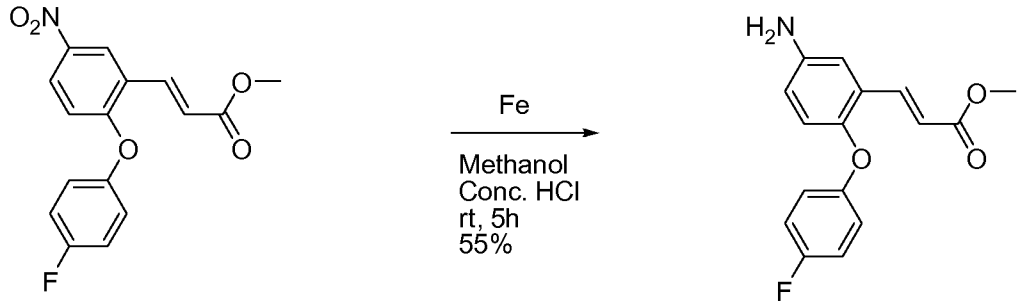
34 35 36

[00383] Step 1: To a solution of 2-fluoro-5-nitro-benzaldehyde (**34**) (676 mg, 4.0 mmol) and 4-fluoroorophenol (**35**) (537 mg, 4.8 mmol) in DMSO (5 mL) was added K_2CO_3 (1.10 g, 8.0 mmol) at room temperature ("rt"). The resulting mixture was flushed with N_2 and heated in a sealed vessel with stirring at 120 °C for 3 h. After the reaction mixture was cooled to rt and poured into brine, the mixture was extracted with ethyl acetate (35 mL x 3). The combined extracts were washed with brine (10 mL x 2), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by a SiO_2 plug (eluted by 15% EtOAc in hexanes) to afford pure 2-(4-fluoro-phenoxy)-5-nitro-benzaldehyde (**36**) (1.05 g, 4.0 mmol, 99%) as a viscous oil. ESI MS m/z 262.2 $(M+H)^+$.



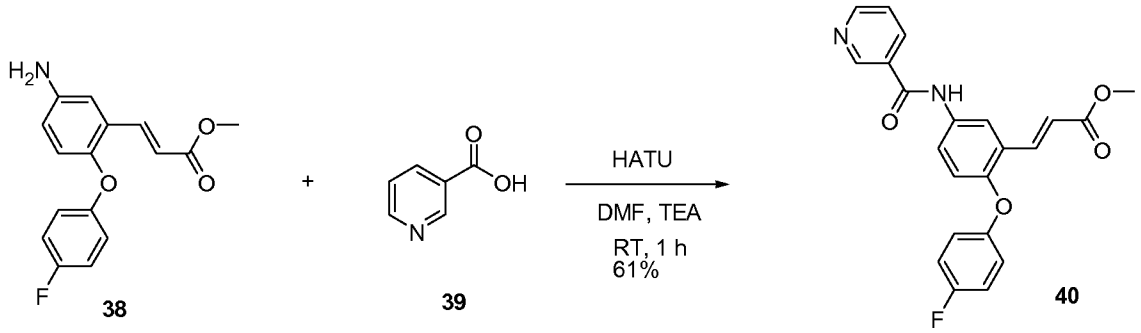
36 37

[00384] Step 2: To a stirred solution of 2-(4-fluoro-phenoxy)-5-nitro-benzaldehyde (**36**) (469 mg, 1.79 mmol) and trimethyl phosphonoacetate (650 mg, 3.58 mmol) in acetonitrile (20 mL) was added LiCl (228 mg, 5.36 mmol), followed by DBU (0.802 mL, 5.36 mmol) at rt. The resulting mixture was stirred at rt for 65 h. After the reaction mixture was concentrated under reduced pressure, the residue was treated with ethyl acetate (100 mL). The EtOAc solution was washed with 1 M HCl aq. (10 mL x 2), sat. $NaHCO_3$ aq. (10 mL), and brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by a SiO_2 plug (eluted by 10% to 25% EtOAc in hexanes) to afford pure 3-[2-(4-fluoro-phenoxy)-5-nitro-phenyl]-acrylic acid methyl ester (**37**) (478 mg, 1.50 mmol, 83%) as a viscous oil. ESI MS m/z 318.3 $(M+H)^+$.



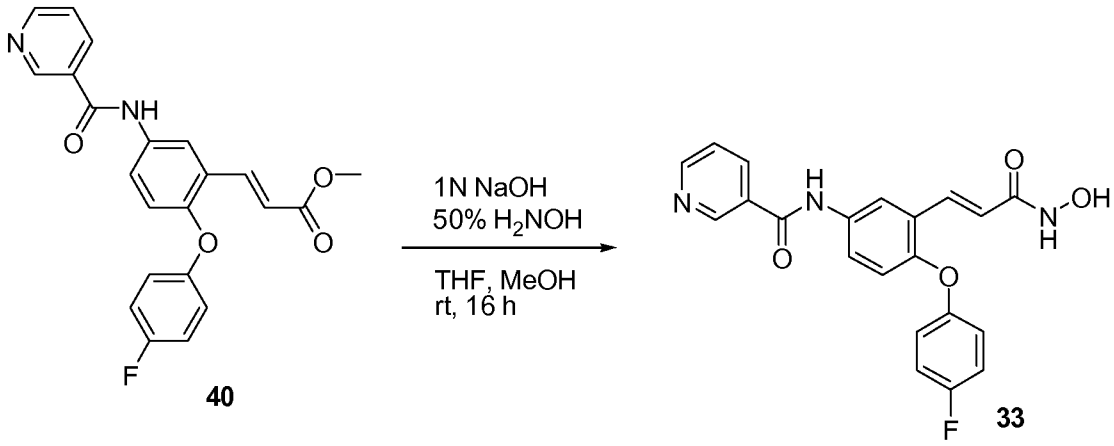
37 38

[00385] Step 3: To a stirred solution of 3-[2-(4-fluoro-phenoxy)-5-nitro-phenyl]-acrylic acid methyl ester (**37**) (478 mg, 1.50 mmol) in methanol (10 mL) was added 412 mg (7.5 mmol) of iron powder. To this mixture 10 mL of conc. HCl was added at room temperature. The resulting mixture was stirred at rt for 5 h and then allowed to stand for 1 h. The reaction mixture was filtered through a Buckner funnel to remove iron powder and the resulting solution was evaporated to dryness. It is then treated with ethyl acetate and washed with aqueous sodium bicarbonate and dilute HCl. The organic layer was separated and the aqueous layer was further extracted with EtOAc (30 mL x 3). The combined organic phases were washed with brine (10 mL x 2), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The 3-[2-(4-fluoro-phenoxy)-5-amino-phenyl]-acrylic acid methyl ester (**38**) was isolated as a yellow oil and used without further purification. ESI MS m/z 288.3 $(M+H)^+$.



38 39 40

[00386] Step 4: To a stirred solution of 3-[2-(4-fluoro-phenoxy)-5-amino-phenyl]-acrylic acid methyl ester (**38**) (58 mg, 0.20 mmol) and 3-pyridyl carboxylic acid (**39**) (35 mg, 0.32 mmol) in DMF (2 mL) was added HATU (114 mg, 0.30 mmol), followed by a solution of TEA (0.033 mL, 0.32 mmol) at rt under N_2. The resulting mixture was stirred for 4 h. After the reaction mixture was concentrated under reduced pressure, the residue was treated with ethyl acetate (75 mL). The solution was washed with acid (HCl) and base ($NaHCO_3$) and brine (10 mL x 2), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by a SiO_2 plug (eluted by 33% to 50% EtOAc in hexanes) to afford 3-{2-(4-fluoro-phenoxy)-5-[(pyridine-3-carbonyl)-amino]-phenyl}-acrylic acid methyl ester (**40**) (47 mg, 0.12 mmol, 61%) as a viscous oil. ESI MS m/z 393.4 $(M+H)^+$.

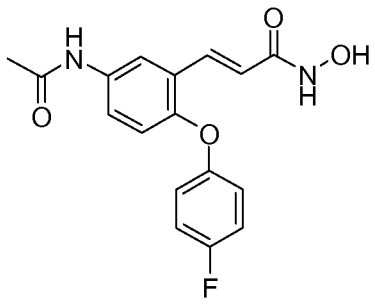


40 33

[00387] Step 5: To a stirred solution of 3-{2-(4-fluoro-phenoxy)-5-[(pyridine-3-carbonyl)-amino]-phenyl}-acrylic acid methyl ester (**40**) (86 mg, 0.22 mmol) in THF (1.2 mL) and MeOH (1.2 mL) was added 50% solution of NH_2OH in water (0.73 mL, 11 mmol) and 1 N NaOH aq. (0.5 mL, 0.5 mmol) at rt. The resulting mixture was stirred at rt for 16 h. After the reaction mixture was concentrated under reduced pressure, the resulting aqueous suspension was diluted with DMSO (1.5 mL) and purified by HPLC to afford N-[4-(4-fluoro-phenoxy)-3-(2-hydroxycarbamoyl-vinyl)-phenyl]-nicotinamide (**33**) (54 mg, 0.14 mmol, 62%) as a white solid. EM (calc): 393.37; ESI MS m/z 394.1 $(M+H)^+$.

Example 29: Synthesis of *(E)*-3-(5-acetamido-2-(4-fluorophenoxy)phenyl)-N-hydroxyacrylamide (41)

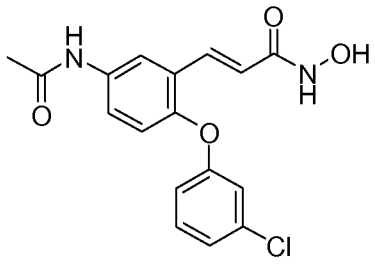
[00388] The title compound was synthesized as described in Example 28. EM (calc): 330.1; MS (M+1H) = 331.0.



41

Example 30: Synthesis of (*E*)-3-(5-acetamido-2-(3-chlorophenoxy)phenyl)-N-hydroxyacrylamide (42)

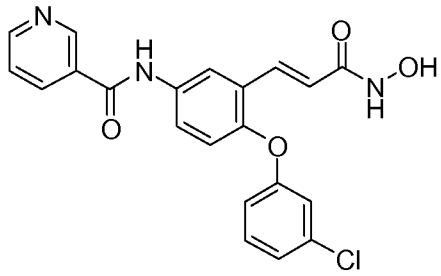
[00389] The title compound was synthesized as described in Example 28. EM (calc): 346.07; MS (M+1H) = 347.0.



42

Example 31: Synthesis of (*E*)-*N*-(4-(3-chlorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide (43)

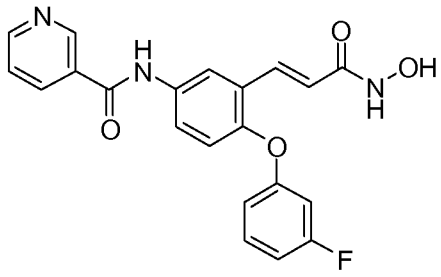
[00390] The title compound was synthesized as described in Example 28. EM (calc): 409.08; MS (M+1H) = 410.5.



43

Example 32: Synthesis of (*E*)-*N*-(4-(3-fluorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide (44)

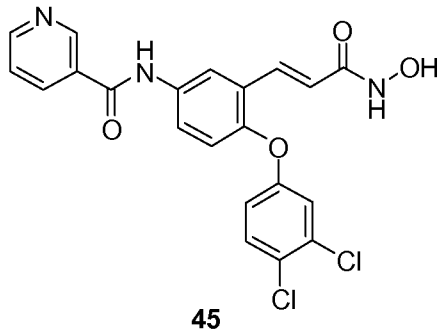
[00391] The title compound was synthesized as described in Example 28. EM (calc): 393.11; MS (M+1H) = 394.0.



44

Example 33: Synthesis of (*E*)-*N*-(4-(3,4-dichlorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide (45)

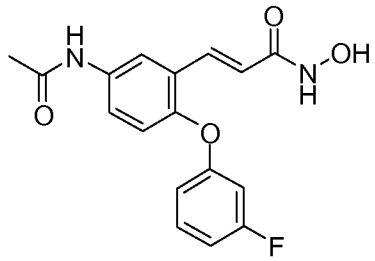
[00392] The title compound was synthesized as described in Example 28. EM (calc): 443.04; MS (M+1H) = 444.5.



45

Example 34: Synthesis of (*E*)-3-(5-acetamido-2-(3-fluorophenoxy)phenyl)-*N*-hydroxyacrylamide (46)

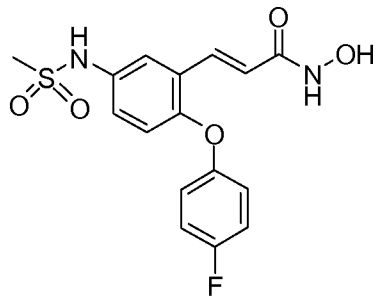
[00393] The title compound was synthesized as described in Example 28. EM (calc): 330.10; MS (M+1H) = 331.0.



46

Example 35: Synthesis of (*E*)-3-(2-(4-fluorophenoxy)-5-(methylsulfonamido)phenyl)-*N*-hydroxyacrylamide (47)

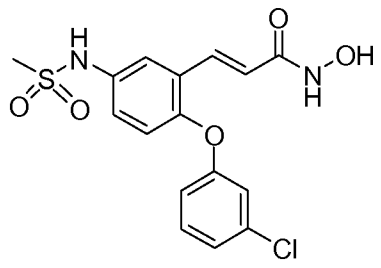
[00394] The title compound was synthesized as described in Example 28. EM (calc): 366.07; MS (M+1H) = 367.0.



47

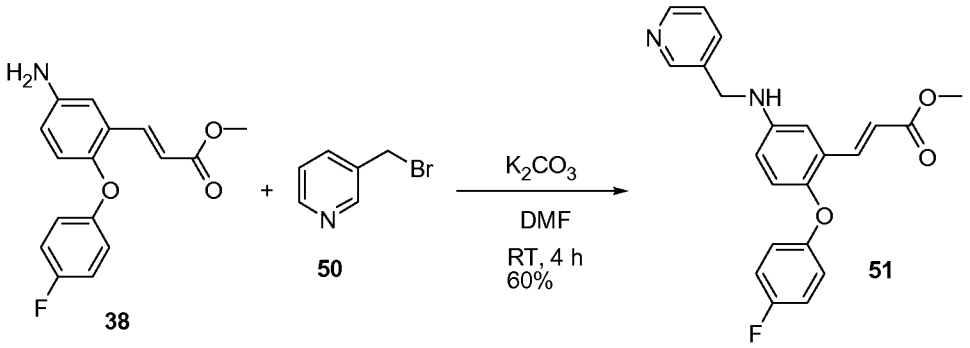
Example 36: Synthesis of (*E*)-3-(2-(3-chlorophenoxy)-5-(methylsulfonamido)phenyl)-*N*-hydroxyacrylamide (48)

[00395] The title compound was synthesized as described in Example 28. EM (calc): 382.04; MS (M+1H) = 383.0.



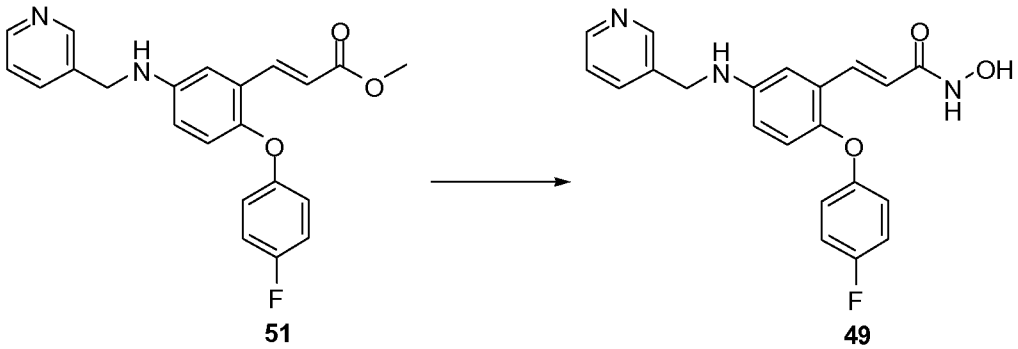
48

Example 37: Synthesis of (*E*)-3-(2-(4-fluorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-*N*-hydroxyacrylamide (49)



38 50 51

[00396] Step 1: To a mixture of 3-[2-(4-fluoro-phenoxy)-5-amino-phenyl]-acrylic acid methyl ester (**38**) (72 mg, 0.22 mmol) and and 3-bromomethyl-pyridine (**50**) (41 mg, 0.24 mmol) was added 3 mL of DMF and 200 mg K_2CO_3 and stirred at rt for 4 h. After the reaction was completed, the mixture was concentrated under reduced pressure, and the residue was treated with ethyl acetate (75 mL). The ethyl acetate solution was washed with acid (HCl) and base ($NaHCO_3$) and brine (10 mL x 2), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by a SiO_2 plug (eluted by 33% to 50% EtOAc in hexanes) to afford (*E*)-methyl 3-(2-(4-fluorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)acrylate (**51**) (46 mg, 0.12 mmol, 61%) as a viscous oil. ESI MS m/z 379.4 $(M+H)^+$.



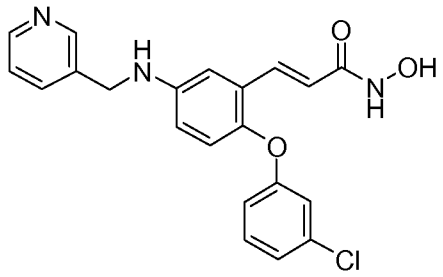
51 49

[00397] Step 2: This compound was prepared from 3-{2-(4-fluoro-phenoxy)-5-[(pyridine-3-ylmethyl)-amino]-phenyl}-acrylic acid methyl ester (**51**) (84 mg, 0.22 mmol) by following the same procedure described in Example 28, step 5, to provide 43 mg (0.10 mmol, 47%) of (*E*)-3-

(2-(4-fluorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-*N*-hydroxyacrylamide (**49**) as a white solid after HPLC purification. EM (calc): 379.13; ESI MS m/z 380.1 $(M+H)^+$.

Example 38: Synthesis of (*E*)-3-(2-(3-chlorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-*N*-hydroxyacrylamide (52)

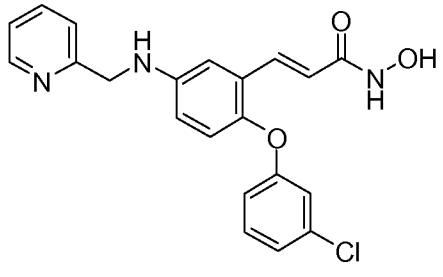
[00398] The title compound was synthesized as described in Example 37. EM (calc): 395.1; MS (M+1H) = 396.1.



52

Example 39: Synthesis of (*E*)-3-(2-(3-chlorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-*N*-hydroxyacrylamide (53)

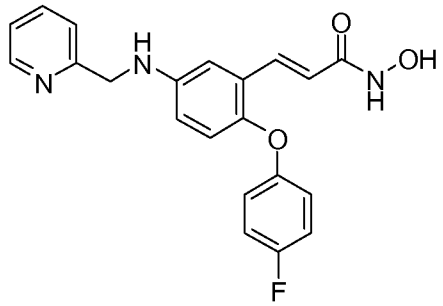
[00399] The title compound was synthesized as described in Example 37. EM (calc): 395.1; MS (M+1H) = 396.0.



53

Example 40: Synthesis of (*E*)-3-(2-(4-fluorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-*N*-hydroxyacrylamide (54)

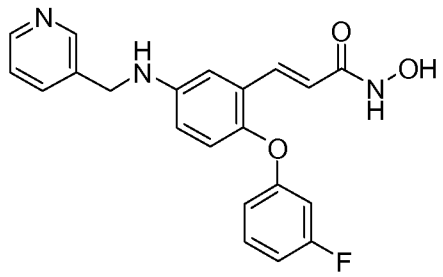
[00400] The title compound was synthesized as described in Example 37. EM (calc): 379.13; MS (M+1H) = 380.5.



54

Example 41: Synthesis of (*E*)-3-(2-(3-fluorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-*N*-hydroxyacrylamide (55)

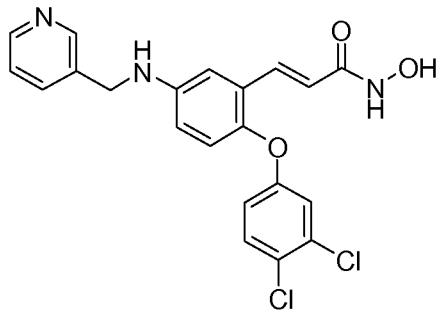
[00401] The title compound was synthesized as described in Example 37. EM (calc): 379.13; MS (M+1H) = 380.0.



55

Example 42: Synthesis of (*E*)-3-(2-(3,4-dichlorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-*N*-hydroxyacrylamide (56)

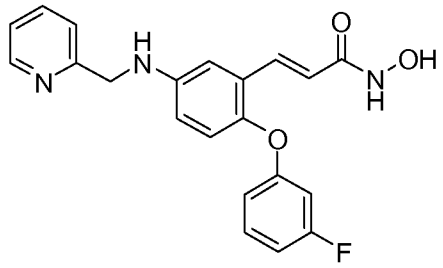
[00402] The title compound was synthesized as described in Example 37. EM (calc): 429.06; MS (M+1H) = 430.5.



56

Example 43: Synthesis of (*E*)-3-(2-(3-fluorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-*N*-hydroxyacrylamide (57)

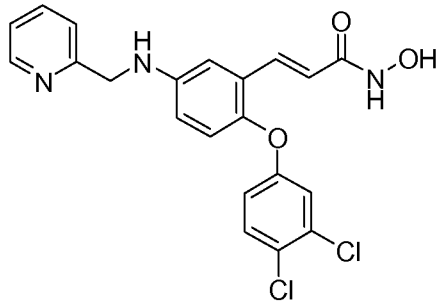
[00403] The title compound was synthesized as described in Example 37. EM (calc): 379.13; MS (M+1H) = 380.5.



57

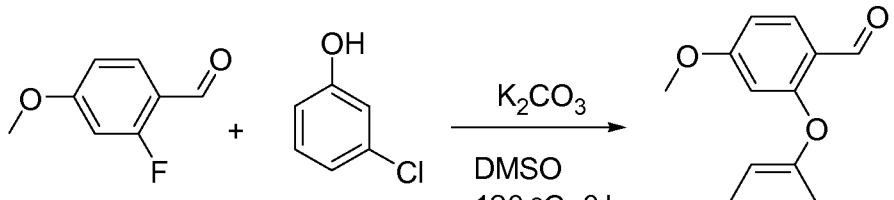
Example 44: Synthesis of (*E*)-3-(2-(3,4-dichlorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-*N*-hydroxyacrylamide (58)

[00404] The title compound was synthesized as described in Example 37. EM (calc): 429.06; MS (M+1H) = 430.0.



58

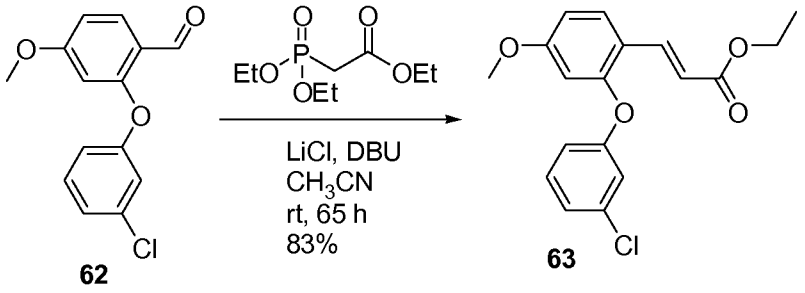
Example 45: Synthesis of (*E*)-3-(2-(3-chlorophenoxy)-4-(pyridin-3-ylmethoxy)phenyl)-*N*-hydroxyacrylamide (59)



60 61 62

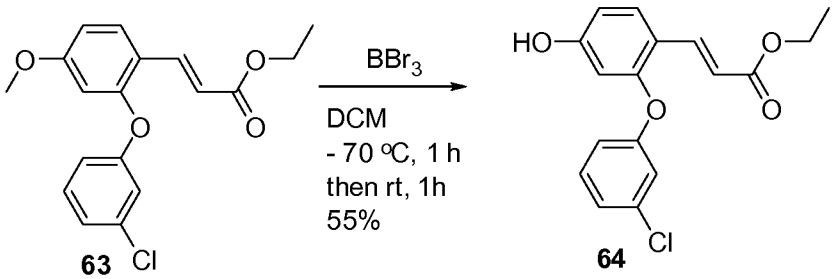
[00405] Step 1: To a solution of 2-fluoro-4-methoxy-benzaldehyde (**60**) (616 mg, 4.0 mmol) and 3-chlorophenol (**61**) (617 mg, 4.8 mmol) in DMSO (5 mL) was added K_2CO_3 (1.10 g, 8.0 mmol) at rt. The resulting mixture was flushed with N_2 and heated in a sealed vessel with stirring at 120 °C for 3 h. After the reaction mixture was cooled to rt and poured into brine, the mixture was extracted with ethyl acetate (35 mL x 3). The combined extracts were washed with brine (10 mL x 2), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by a SiO_2 plug (eluted by 15% EtOAc in hexanes) to afford 2-(3-chlorophenoxy)-4-

methoxybenzaldehyde (**62**) (1.05 g, 4.0 mmol, 99%) as a viscous oil. ESI MS m/z 263.1 $(M+H)^+$.



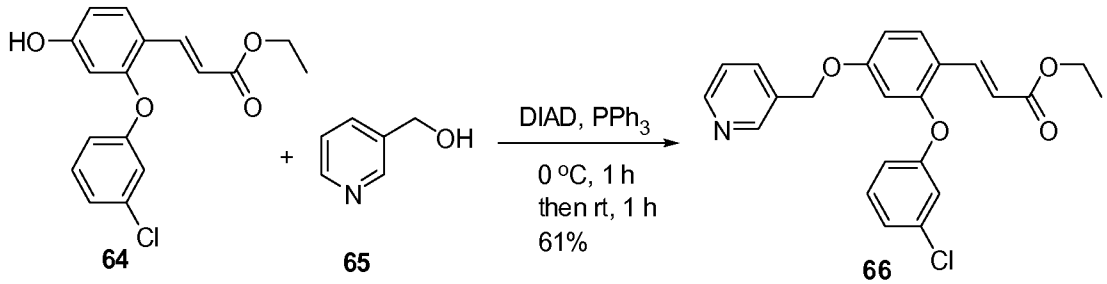
62 63

[00406] Step 2: To a stirred solution of 2-(3-chloro-phenoxy)-4-methoxy-benzaldehyde (**62**) (469 mg, 1.79 mmol) and triethyl phosphonoacetate (803 mg, 3.58 mmol) in acetonitrile (20 mL) was added LiCl (228 mg, 5.36 mmol), followed by DBU (0.802 mL, 5.36 mmol) at rt. The resulting mixture was stirred at rt for 65 h. After the reaction mixture was concentrated under reduced pressure, the residue was treated with ethyl acetate (100 mL). The EtOAc solution was washed with 1 M HCl aq. (10 mL x 2), sat. $NaHCO_3$ aq. (10 mL), and brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by a SiO_2 plug (eluted by 10% to 25% EtOAc in hexanes) to afford (*E*)-ethyl 3-(2-(3-chlorophenoxy)-4-methoxyphenyl)acrylate (**63**) (498 mg, 1.50 mmol, 83%) as a viscous oil. ESI MS m/z 333.3 $(M+H)^+$.

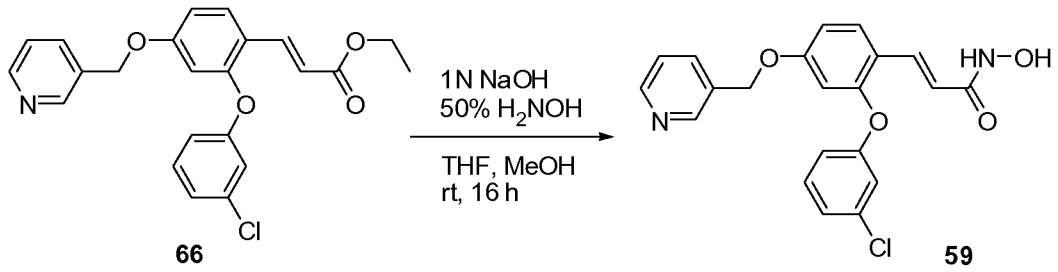


63 64

[00407] Step 3: To a stirred solution of 3-[2-(3-chloro-phenoxy)-4-methoxy-phenyl]-acrylic acid ethyl ester (**63**) (498 mg, 1.50 mmol) in DCM (10 mL) was added 1 M solution of BBr_3 in DCM (4.5 mL, 4.5 mmol) at -70 °C under N_2. The resulting mixture was stirred at -70 °C for 1 h and then allowed to warm to rt. After the reaction mixture was stirred at rt for another hour, the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (10 mL) slowly at 0 °C. The mixture was transferred into a separation funnel and the organic layer was separated. The aqueous layer was further extracted with DCM (30 mL x 3). The combined organic phases were washed with brine (10 mL x 2), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by a SiO_2 plug (eluted by 10% to 25% EtOAc in hexanes) to afford (*E*)-ethyl 3-(2-(3-chlorophenoxy)-4-hydroxyphenyl)acrylate (**64**) (267 mg, 0.84 mmol, 56%) as an off-white powder. ESI MS m/z 318.9 $(M+H)^+$.



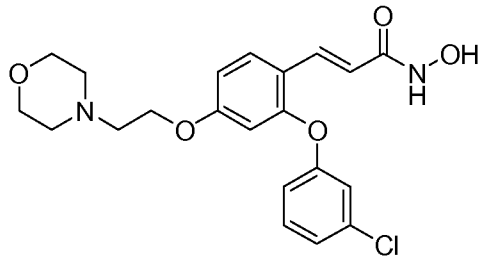
[00408] Step 4: To a stirred solution of 3-[2-(3-chloro-phenoxy)-4-hydroxy-phenyl]-acrylic acid ethyl ester (**64**) (64 mg, 0.20 mmol) and 3-pyridylcarbinol (**65**) (35 mg, 0.32 mmol) in THF (2 mL) was added Ph_3P (79 mg, 0.30 mmol), followed by a solution of DIAD (0.063 mL, 0.32 mmol) in THF (1 mL) at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 1 h and then at rt for 16 h. After the reaction mixture was concentrated under reduced pressure, the residue was treated with ethyl acetate (75 mL). The solution was washed with brine (10 mL x 2), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by a SiO_2 plug (eluted by 33% to 50% EtOAc in hexanes) to afford (*E*)-ethyl 3-(2-(3-chlorophenoxy)-4-(pyridin-3-ylmethoxy)phenyl)acrylate (**66**) (50 mg, 0.12 mmol, 61%) as a viscous oil. ESI MS m/z 410.2 $(M+H)^+$.



[00409] Step 5: To a stirred solution of 3-[2-(3-chloro-phenoxy)-4-(pyridin-3-ylmethoxy)-phenyl]-acrylic acid ethyl ester (**66**) (91 mg, 0.22 mmol) in THF (1.2 mL) and MeOH (1.2 mL) was added 50% solution of NH_2OH in water (0.73 mL, 11 mmol) and 1 N NaOH aq. (0.5 mL, 0.5 mmol) at rt. The resulting mixture was stirred at rt for 16 h. After the reaction mixture was concentrated under reduced pressure, the resulting aqueous suspension was diluted with DMSO (1.5 mL) and purified by HPLC to afford (*E*)-3-(2-(3-chlorophenoxy)-4-(pyridin-3-ylmethoxy)phenyl)-*N*-hydroxyacrylamide (**59**) (54 mg, 0.14 mmol, 62%) as a white solid. EM (calc): 396.09; ESI MS m/z 397.5 $(M+H)^+$.

Example 46: Synthesis of (*E*)-3-(2-(3-chlorophenoxy)-4-(2-morpholinoethoxy)phenyl)-*N*-hydroxyacrylamide (67)

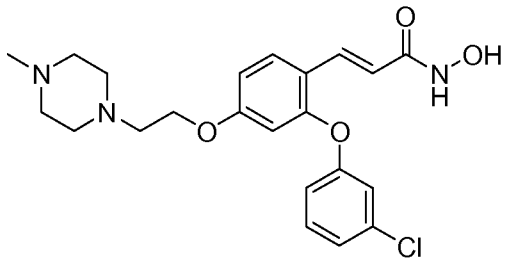
[00410] The title compound was synthesized as described in Example 45. EM (calc): 418.13; MS (M+1H) = 419.5.



67

Example 47: Synthesis of (*E*)-3-(2-(3-chlorophenoxy)-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-*N*-hydroxyacrylamide (68)

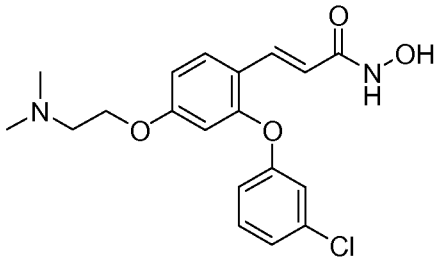
[00411] The title compound was synthesized as described in Example 45. EM (calc): 431.16; MS (M+1H) = 432.5.



68

Example 48: Synthesis of (*E*)-3-(2-(3-chlorophenoxy)-4-(2-(dimethylamino)ethoxy)phenyl)-*N*-hydroxyacrylamide (69)

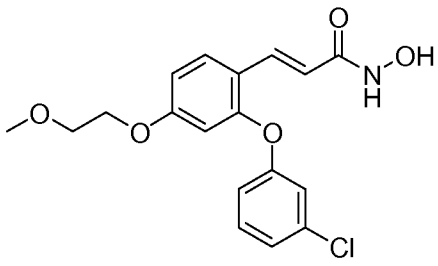
[00412] The title compound was synthesized as described in Example 45. EM (calc): 376.12; MS (M+1H) = 377.5.



69

Example 49: Synthesis of (*E*)-3-(2-(3-chlorophenoxy)-4-(2-methoxyethoxy)phenyl)-*N*-hydroxyacrylamide (70)

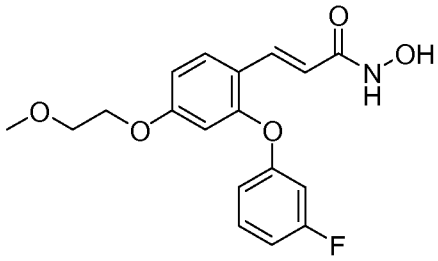
[00413] The title compound was synthesized as described in Example 45. EM (calc): 363.09; MS (M+1H) = 364.5.



70

Example 50: Synthesis of (*E*)-3-(2-(3-fluorophenoxy)-4-(2-methoxyethoxy)phenyl)-*N*-hydroxyacrylamide (71)

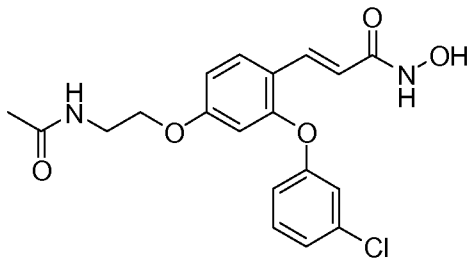
[00414] The title compound was synthesized as described in Example 45. EM (calc): 347.12; MS (M+1H) = 348.0.



71

Example 51: Synthesis of (*E*)-3-(4-(2-acetamidoethoxy)-2-(3-chlorophenoxy)phenyl)-*N*-hydroxyacrylamide (72)

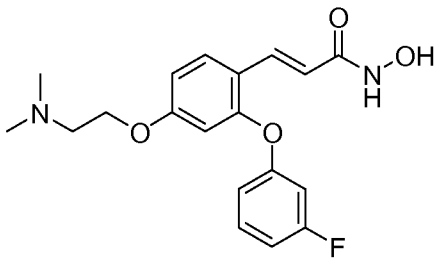
[00415] The title compound was synthesized as described in Example 45. EM (calc): 390.09; MS (M+1H) = 391.5.



72

Example 52: Synthesis of (*E*)-3-(2-(3-fluorophenoxy)-4-(2-(dimethylamino)ethoxy)phenyl)-*N*-hydroxyacrylamide (73)

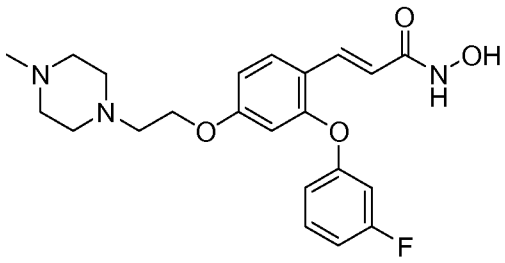
[00416] The title compound was synthesized as described in Example 45. EM (calc): 360.14; MS (M+1H) = 361.0.



73

Example 53: Synthesis of (*E*)-3-(2-(3-fluorophenoxy)-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-*N*-hydroxyacrylamide (74)

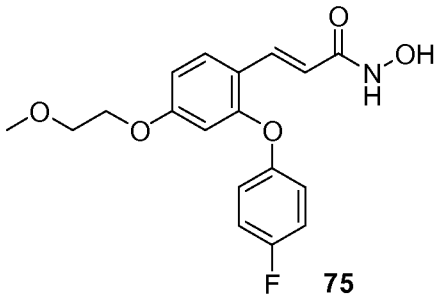
[00417] The title compound was synthesized as described in Example 45. EM (calc): 415.19; MS (M+1H) = 416.5.



74

Example 54: Synthesis of (*E*)-3-(2-(4-fluorophenoxy)-4-(2-methoxyethoxy)phenyl)-*N*-hydroxyacrylamide (75)

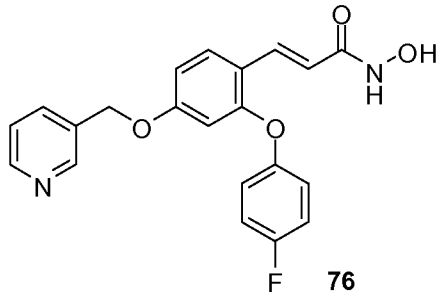
[00418] The title compound was synthesized as described in Example 45. EM (calc): 347.12; MS (M+1H) = 348.0.



75

Example 55: Synthesis of (*E*)-3-(2-(4-fluorophenoxy)-4-(pyridin-3-ylmethoxy)phenyl)-*N*-hydroxyacrylamide (76)

[00419] The title compound was synthesized as described in Example 45. EM (calc): 380.11; MS (M+1H) = 381.5.



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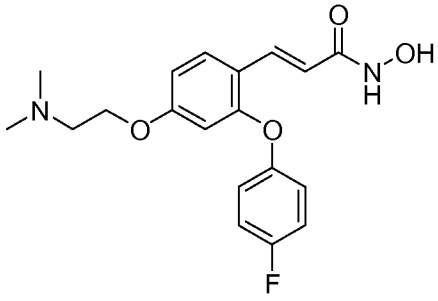
Example 56: Synthesis of (*E*)-3-(2-(4-fluorophenoxy)-4-(2-(dimethylamino)ethoxy)phenyl)-*N*-hydroxyacrylamide (77)

[00420] The title compound was synthesized as described in Example 45. EM (calc): 360.14; MS (M+1H) = 361.5.



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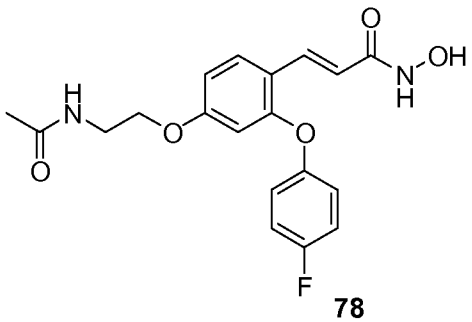
Example 57: Synthesis of (*E*)-3-(4-(2-acetamidoethoxy)-2-(4-fluorophenoxy)phenyl)-*N*-hydroxyacrylamide (78)

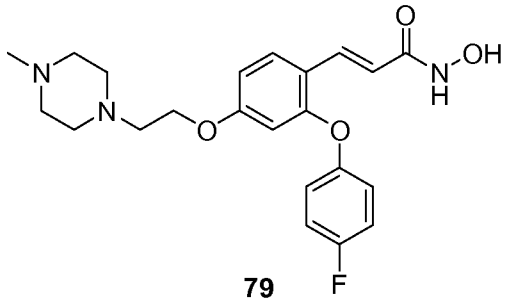
[00421] The title compound was synthesized as described in Example 45. EM (calc): 374.12; MS (M+1H) = 375.0.



78

Example 58: Synthesis of (*E*)-3-(2-(4-fluorophenoxy)-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-*N*-hydroxyacrylamide (79)

[00422] The title compound was synthesized as described in Example 45. EM (calc): 415.19; MS (M+1H) = 416.5.



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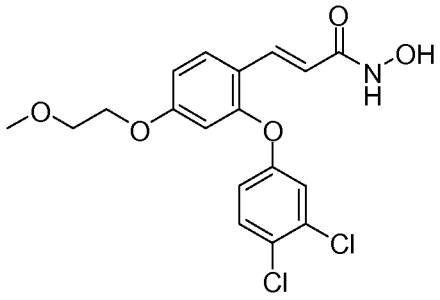
Example 59: Synthesis of (*E*)-3-(2-(3,4-dichlorophenoxy)-4-(2-methoxyethoxy)phenyl)-*N*-hydroxyacrylamide (80)

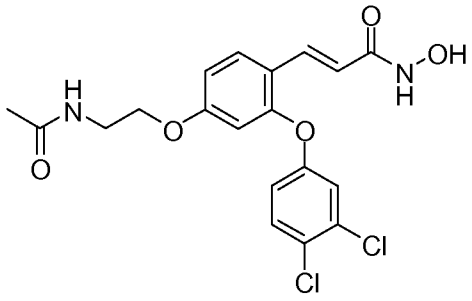
[00423] The title compound was synthesized as described in Example 45. EM (calc): 397.04; MS (M+1H) = 398.0.



80

Example 60: Synthesis of (*E*)-3-(4-(2-acetamidoethoxy)-2-(3,4-dichlorophenoxy)phenyl)-*N*-hydroxyacrylamide (81)

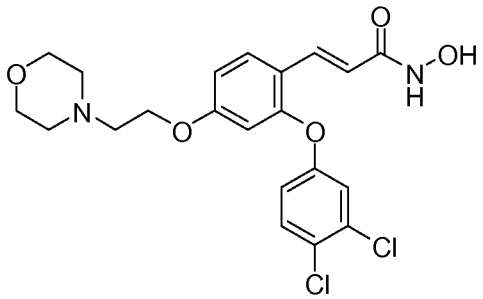
[00424] The title compound was synthesized as described in Example 45. EM (calc): 424.05; MS (M+1H) = 425.0.



81

Example 61: Synthesis of (*E*)-3-(2-(3,4-dichlorophenoxy)-4-(2-morpholinoethoxy)phenyl)-*N*-hydroxyacrylamide (82)

[00425] The title compound was synthesized as described in Example 45. EM (calc): 452.09; MS (M+1H) = 453.0.



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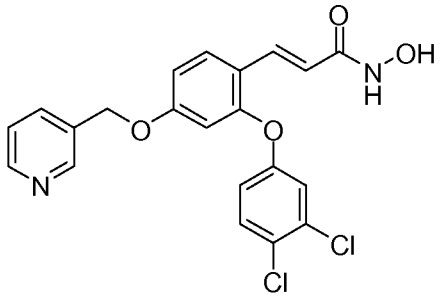
Example 62: Synthesis of (*E*)-3-(2-(3,4-dichlorophenoxy)-4-(pyridin-3-ylmethoxy)phenyl)-*N*-hydroxyacrylamide (83)

[00426] The title compound was synthesized as described in Example 45. EM (calc): 430.04; MS (M+1H) = 431.5.



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Biological Examples

Cell lines and reagents

[00427] Cell lines are obtained from DSMZ (Braunschweig, Germany) or ATCC (Manassas, VA). Cells are grown in RPMI 1640 with 10% fetal bovine serum in a 5% CO_2/air incubator at 37°C. Thapsigargin and BAPTA-AM are from Calbiochem (San Diego, CA). 3-((dimethylamino)methyl)-*N*-(2-(4-(hydroxycarbamoyl)phenoxy)ethyl)benzofuran-2-carboxamide is a broad-spectrum HDAC inhibitor which was synthesized as previously described. Other analogs with varying degrees of specificity towards the HDAC isoforms are synthesized as described herein.

Example 63: Histone Deacetylase Activity

[00428] HDAC activity is measured using a continuous trypsin-coupled assay that has been described in detail previously (US 20070281934; Schultz *et. al.*, *Biochemistry*, 43 (34), 11083 - 11091, 2004; Kim *et al.* (2006), *Methods Mol Biol.*, 325:273-283). For inhibitor characterization, measurements are performed in a reaction volume of 100 □L using 96-well assay plates in a fluorescence plate reader. For each isozyme, the HDAC protein in reaction buffer (50 mM HEPES, 100 mM KCl, 0.001% Tween-20, 5% DMSO, pH 7.4, supplemented with bovine serum albumin at concentrations of 0-0.05%, is mixed with inhibitor at various concentrations and

allowed to incubate for 15 minutes. Trypsin is added to a final concentration of 50 nM, and acetyl-Gly-Ala-(*N*-acetyl-Lys)-AMC is added to a final concentration of 25-100 μM to initiate the reaction. After a 30 minute lag time, the fluorescence is measured over a 30 minute time frame using an excitation wavelength of 355 nm and a detection wavelength of 460 nm. The increase in fluorescence with time is used as the measure of the reaction rate. Inhibition constants K_i(app) were obtained using the program BatchKi (Biokin, Pullman, WA). The results are summarized in Table B below.

Table B. Comparison of HDAC IC_{50} values of Representative HDAC8-selective inhibitors

Compound No.	**HDAC1 IC_{50} (μM)**	**HDAC8 IC_{50} (μM)**	**HDAC6 IC_{50} (μM)**
6	C	A	C
7	C	A	B
8	C	A	B
9	C	A	C
10	C	A	B
11	C	A	B
12	C	A	C
13	C	A	C
14	C	A	C
15	C	A	B
16	C	A	C
17	D	A	D
20	C	A	C
42	D	A	D
49	D	A	C
59	C	A	B
67	C	A	B
68	C	A	B
69	B	A	B
80	D	A	C

A = less than or equal to 0.1 μM

B = greater than 0.1 μM but less than or equal to 1 μM

C = greater than 1 μM but less than or equal to 10 μM

D = greater than 10 μM

Example 64: Cell proliferation assay

[00429] Tumor cell lines and human umbilical vein endothelial cells (HUVEC) are cultured for at least two doubling times, and growth is monitored at the end of compound exposure using an Alamar Blue™ (Biosource, Camarillo, CA) fluorometric cell proliferation assay as recommended by the manufacturer. Compounds are assayed in triplicate wells in 96-well plates. The concentration required to inhibit cell growth by 50% (GI_{50}) and 95% confidence intervals are estimated from nonlinear regression using a 4-parameter logistic equation. The effect of HDAC8 selective inhibitor compounds on cell proliferation in Jurkat cells is measured. Apoptosis is measured by Annexin-V flow cytommetry. Growth inhibiton iss measured by Alamar Blue assay. Growth Inhibition of Jurkat Cells measured by Alamar Blue assay is shown in Table C. Cells are treated with compound for 3 days.

Table C. Growth Inhibition of Jurkat Cells measured by Alamar Blue assay

Compound	GI_{50} (μM)
6	1.43
7	--
8	6.1
9	2.00
10	2.25
11	1.98
12	1.80
13	2.5
14	3.58
15	3.37
16	>20
17	--
20	9.70

Example 65: Western Blotting

[00430] Cells are washed with PBS and resuspended in triple-detergent lysis buffer [50 mM Tris-Cl (pH 8.0), 150 mM NaCl, 0.1% SDS, 0.5% deoxycholic acid, 1.0% NP-40, supplemented with 1mM EDTA, 1 mM PMSF, 1mM Na_3VO_4, 2mM β-glycerophosphate and the COMPLETE protease inhibitor cocktail (Roche Molecular Biochemicals, Indianapolis, IN)] on ice for 10 minutes. After centrifugation, equal quantities of protein are resolved on SDS-polyacrylamide gels (Bio-Rad Laboratories, Hercules, CA). Gels are transferred to polyvinylidene difluoride membrane using a Semi-dry Transfer Cell (Bio-Rad Laboratories, Hercules, CA) and Western blotted, using an anti-Hsc70 antibody to control for loading and transfer. Bands are imaged and quantified in the linear range and normalized to Hsc70, using the Odyssey Infrared Imaging System (LICOR, Lincoln, NE).

Example 66: Apoptosis assays

[00431] Cytotoxicity is evaluated after 2 or 3 days of treatment with inhibitor alone and in combination with qVD, BAPTA-AM, thapsigargin and phospholipase C inhibitor using annexin-V staining. Annexin-V binding is assayed with a FACSCalibur instrument (Becton-Dickinson, San Jose, CA) using reagents from BioVision (Mountain View, CA) per manufacturer's protocol.

Example 67: Caspase activation assays

[00432] Caspase enzyme activity iss measured in Jurkat cells using the Apotarget Caspase Colorimetric Protease Assay (BioSource International, Camarillo, CA) as per manufacturer's protocol following treatment with inhibitor.

Example 68: Intracellular Calcium Measurements

[00433] For the spectrofluorimetric measurements, cells (1 X 10^6 cells/mL) are incubated for 1 h in Hanks' Balanced Salt Solution (HBSS; Invitrogen) containing 10% Fetal Bovine Serum and 5 □M Indo1-AM (Invitrogen) at 37°C in the dark. Cells are then harvested, centrifuged (200 X g for 5 min) and washed three times with HBSS to remove extracellular Indo1, and readjusted to 1 X 10^6 cells/mL in HBSS. Fluorescence is monitored throughout each experiment at 37°C with a fluorescent plate reader (Fluoroskan Ascent FL; Thermo Scientific). After a 5 min temperature equilibration period, samples are excited at 338nm and emission is collected at 405 and 485nm, corresponding to the Ca^{2+}-bound and -free Indo1 fluorescence emitted respectively, at 6-sec intervals over a 1 minute period. Drug (or control) is then added, and acquisition is continued for 5 minutes. Maximal ratio values are determined by the addition of 10□M ionomycin at the end of the measurements. Intracellular [Ca^{2+}] changes are shown as changes in the ratio of Ca^{2+}-bound and -free Indo1.

Example 69: Pharmacokinetic Analysis of HDAC Inhibitor Compounds

[00434] This study, performed in male rats with test compounds is designed to provide preliminary information on their pharmacokinetics. The test compounds are administered in combination by oral gavage.

[00435] The specifications for rats used on this study are as follows:

Strain: CD® IGS rats (Sprague-Dawley derived)

Source: Charles River Laboratories

Surgical modification for oral dosing: One portal vein cannula and one jugular vein cannula

Body weight range at dosing 350 to 375 g

[00436] The rats are acclimatized to laboratory conditions for at least 24 hours before dosing. The evening before dosing, food is withheld from the rats and is returned immediately following

the 3-hour blood collection time point. Water is provided *ad libitum*. The rats are housed individually in translucent polycarbonate cages.

[00437] Test compounds are prepared as 3.0 mg/ml solutions (1% MC/0.4% Cr EL in WFI).

[00438] Rats are administered a single dose of test compound in combination by oral gavage. Dose volumes are adjusted based on body weight data collected immediately prior to dosing.

[00439] The dose volume is 1 ml/kg and the nominal dosage is 3 mg/kg.

[00440] Blood samples are collected at 5 minutes, 20 minutes, 1 hour, 3 hours, 6 hours, 9 hours, and 24 hours post-dosing from orally dosed rats. The samples are collected into plasma separator Microtainer tubes with anticoagulant (lithium heparin). Plasma samples are prepared by centrifugation (5 min at 5000 x g), and at least 100 μL are transferred to storage tubes and frozen on dry ice. Samples are maintained at approximately -75C until prepared for analysis.

[00441] Plasma samples are thawed and 75 uL aliquots are transferred to centrifuge tubes to which 10 μL aliquots of internal standard solution (0.5 μg/mL) are added. The samples are not diluted with blank plasma prior to further processing. Soluble proteins are precipitated by the addition of 300 μL of methanol, followed by centrifugation (20 min at 16,000 x g). The samples are evaporated to dryness and reconstituted in 100 μL of water containing 0.2% formic acid and 10% methanol. All amples are loaded onto an autosampler maintained at 6 °C and evaluated for oncentrations of test compound using LC-MS/MS. Plasma concentration data are evaluated using the computer program WinNonlin (Professional Edition, Pharsight Corporation, version 5.01). The analyses are performed using nominal sample times and a noncompartmental method with uniform weighting. Pharmacokinetic parameter estimates include terminal half-life, volume of distribution at steady state, and area under the concentration-time curve (AUC).

[00442] HDAC inhibitor 3-((dimethylamino)methyl)-*N*-(2-(4-(hydroxycarbamoyl)phenoxy)ethyl)benzofuran-2-carboxamide is added to the cassette to serve as a standard since the pharmacokinetics of this compound have been determined previously in rats.

Example 70a: Parenteral Composition

[00443] To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a selective HDAC8 inhibitor compound described herein is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

[00444] In another embodiment, the following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
Selective HDAC8 inhibitor compound described herein	1.2 g
sodium acetate buffer solution (0.4 M)	2.0 mL
HCl (1 N) or NaOH (1 M)	q.s. to suitable pH
water (distilled, sterile)	q.s.to 20 mL

[00445] All of the above ingredients, except water, are combined and heated to 60-70 °C with stirring. A sufficient quantity of water at 60 °C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Example 70b: Oral Composition

[00446] To prepare a pharmaceutical composition for oral delivery, 100 mg of a selective HDAC8 inhibitor compound described herein is mixed with 750 mg of starch. The mixture is incorporated into an oral dosage unit for, such as a hard gelatin capsule, which is suitable for oral administration.

[00447] In another embodiment, the following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
selective HDAC8 inhibitor compound described herein	400
Cornstarch	50
croscarmellose sodium	25
Lactose	120
magnesium stearate	5

[00448] In yet another embodiment, the following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per tablet, mg
selective HDAC8 inhibitor compound described herein	200
lactose, spray-dried	148
magnesium stearate	2

[00449] In yet another embodiment, the following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
selective HDAC8 inhibitor compound described herein	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 mL
Colorings	0.5 mg
distilled water	q.s. to 100 mL

Example 70c: Sublingual (Hard Lozenge) Composition

[00450] To prepare a pharmaceutical composition for buccal delivery, such as a hard lozenge, mix 100 mg of a selective HDAC8 inhibitor compound described herein with 420 mg of powdered sugar mixed, with 1.6 mL of light corn syrup, 2.4 mL distilled water, and 0.42 mL mint extract. The mixture is gently blended and poured into a mold to form a lozenge suitable for buccal administration.

Example 70d: Inhalation Composition

[00451] To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a selective HDAC8 inhibitor compound described herein is mixed with 50 mg of anhydrous citric acid and

100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

Example 70e: Rectal Gel Composition

[00452] To prepare a pharmaceutical composition for rectal delivery, 100 mg of a selective HDAC8 inhibitor compound described herein is mixed with 2.5 g of methylcelluose (1500 mPa), 100 mg of methylparapen, 5 g of glycerin and 100 mL of purified water. The resulting gel mixture is then incorporated into rectal delivery units, such as syringes, which are suitable for rectal administration.

Example 70f: Suppository Formulation

[00453] A suppository of total weight 2.5 g is prepared by mixing a selective HDAC8 inhibitor compound described herein with Witepsol™ H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

Ingredient	Quantity per suppository (mg)
selective HDAC8 inhibitor compound described herein	500
Witepsol® H-15	balance

Example 70g: Topical Gel Composition

[00454] To prepare a pharmaceutical topical gel composition, 100 mg of a selective HDAC8 inhibitor compound described herein is mixed with 1.75 g of hydroxypropyl celluose, 10 mL of propylene glycol, 10 mL of isopropyl myristate and 100 mL of purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topicl administration.

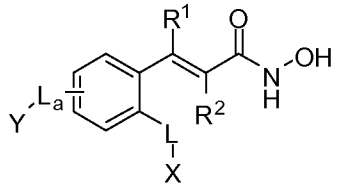
Example 70h: Ophthalmic Solution Composition

[00455] To prepare a pharmaceutical opthalmic solution composition, 100 mg of a selective HDAC8 inhibitor compound described herein is mixed with 0.9 g of NaCl in 100 mL of purified water and filterd using a 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

[00456] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes are to be included within the spirit and purview of disclosure and scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound having a structure of Formula I:



Formula I

wherein:

$R^1$and R^2 are each independently H, OH, halogen, or C_1-C_6alkyl;

L and L_a are each independently a bond, O, S, NR^3, -$NR^{10}C(=O)$-R^{11}, S(=O), $S(=O)_2$, $NHS(=O)_2$, -C_1-C_6alkylene-, -C_2-C_6alkenylene-, -C_2-C_6alkynylene-, -C_1-C_6heteroalkylene-, -C_1-C_6alkylene-O-, -C_1-C_3alkylene-O-C_1-C_3alkylene-, -C_1-C_6alkylene-NR^3-, -C_1-C_3alkylene-NR^3-C_1-C_3alkylene -, -C_1-C_6alkylene-$C(=O)NR^3$-, -C_1-C_3alkylene-$C(=O)NR^3$-C_1-C_3alkylene -, -C_1-C_6alkylene-$NR^3C(=O)$-, -C_1-C_3alkylene-$NR^3C(=O)$-C_1-C_3alkylene-, -C_1-C_6alkylene-S-, -C_1-C_3alkylene-S-C_1-C_3alkylene-, -C_1-C_6alkylene-S(=O)-, -C_1-C_3alkylene-S(=O)-C_1-C_3alkylene, -C_1-C_6alkylene-$S(=O)_2$-, -C_1-C_3alkylene-$S(=O)_2$-C_1-C_3alkylene,–C(=O)-, or –C(=O)-C_1-C_6alkylene;

X is a substituted or unsubstituted group selected from among aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if X is substituted, then X is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -$C(=O)R^{11}$, -S-R^{11}, -$S(=O)$-R^{11}, -$S(=O)_2$-R^{11}, -$NR^{10}C(=O)$-R^{11}, -$C(=O)N(R^{10})_2$, -$S(=O)_2N(R^{10})_2$, -$NR^{10}S(=O)_2$-R^{11}, -$OC(=O)N(R^{10})_2$, -$NR^{10}C(=O)O$-R^{11}, -$OC(=O)O$-R^{11}, -$NHC(=O)NH$-R^{11}, -$OC(=O)$-R^{11}, -$N(R^{10})_2$, -C_1-C_2alkyl$N(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

Y is H or a substituted or unsubstituted group selected from among C_1-C_6alkyl, -CO_2R^{10}, -$C(=O)R^{11}$, -$NR^{10}C(=O)$-R^{11}, -$C(=O)N(R^{10})_2$, aryl, heteroaryl, C_3-C_{10}cycloalkyl, and C_2-C_{10}heterocycloalkyl; where if Y is substituted, then Y is substituted with 1, 2, 3, 4, or 5 groups selected from among halogen, C_1-C_6alkoxy, C_1-C_6fluoroalkoxy, aminoC_1-C_6alkoxy, C_1-C_3alkylaminoC_1-C_3alkoxy, hydroxyC_1-C_3alkylaminoC_1-C_3alkoxy, C_2-

C_8heterocycloalkylC_1-C_3alkoxy, C_2-C_8heterocycloalkylC_1-C_2alkyl, -CN, -NO_2, -CO_2R^{10}, -$C(=O)R^{11}$, -S-R^{11}, -$S(=O)$-R^{11}, -$S(=O)_2$-R^{11}, -$NR^{10}C(=O)$-R^{11}, -$C(=O)N(R^{10})_2$, -$S(=O)_2N(R^{10})_2$, -$NR^{10}S(=O)_2$-R^{11}, -$OC(=O)N(R^{10})_2$, -$NR^{10}C(=O)O$-R^{11}, -$OC(=O)O$-R^{11}, -$NHC(=O)NH$-R^{11}, -$OC(=O)$-R^{11}, -$N(R^{10})_2$, -C_1-C_2alkyl$N(R^{10})_2$, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^{10} is hydrogen, or a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6heteroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^{11} is a substituted or unsubstituted group selected from among C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_8cycloalkyl, C_2-C_8heterocycloalkyl, aryl, and heteroaryl;

R^3 is H, C_1-C_6alkyl, phenyl or benzyl;

or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

2. The compound of claim 1 wherein R^1 and R^2 are each independently H.
3. The compound of claim 1 or 2 wherein L is O or S.
4. The compound of any one of claims 1-3 wherein X is a substituted or unsubstituted aryl.
5. The compound of claim 4 wherein aryl is phenyl.
6. The compound of claim 5 wherein phenyl is substituted with at least one Cl, Br, I, or F.
7. The compound of claim 5 wherein phenyl is substituted with at least two of Cl, Br, I, or F.
8. The compound of claim 5 wherein phenyl is substituted with at least one C_1-C_6alkyl.
9. The compound of claim 8 wherein C_1-C_6alkyl is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl.
10. The compound of claim 9 wherein C_1-C_6alkyl is methyl.
11. The compound of claim 5 wherein phenyl is substituted with at least one C_1-C_6alkoxy.
12. The compound of claim 11 wherein C_1-C_6alkoxy is selected from methoxy or ethoxy.
13. The compound of any one of claims 1-3 wherein X is a substituted or unsubstituted heteroaryl.
14. The compound of claim 13 wherein heteroaryl is pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, 4-azaindolyl, 5-azaindolyl, 6-azaindolyl, 7-azaindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl,

thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl.

15. The compound of claim 14 wherein heteroaryl is pyridinyl.
16. The compound of any one of claims 1-3 wherein X is a substituted or unsubstituted C_3-C_{10}cycloalkyl.
17. The compound claim 16 wherein C_3-C_{10}cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.
18. The compound of any one of claims 1-3 wherein X is a substituted or unsubstituted C_2-C_{10}heterocycloalkyl.
19. The compound of claim 18 wherein C_2-C_{10}heterocycloalkyl is quinolizinyl, dioxinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiazinyl, tetrahydropyridinyl, piperazinyl, oxazinanonyl, dihydropyrrolyl, dihydroimidazolyl, tetrahydrofuranyl, tetrahydropyranyl, dihydrooxazolyl, oxiranyl, pyrrolidinyl, pyrazolidinyl, dihydrothienyl, imidazolidinonyl, pyrrolidinonyl, dihydrofuranonyl, dioxolanonyl, thiazolidinyl, piperidinonyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and tetrahydrothienyl.
20. The compound of claim 19 wherein C_2-C_{10}heterocycloalkyl is piperidinyl.
21. The compound of claim 20 wherein piperidinyl is substituted with $-CO_2R^{10}$, $-C(=O)R^{11}$ or $-C(=O)N(R^{10})_2$.
22. The compound of claim 21 wherein piperidinyl is substituted with $-C(=O)R^{11}$.
23. The compound of claim 22 wherein R^{11} is a substituted or unsubstituted C_1-C_6alkyl.
24. The compound of claim 23 wherein C_1-C_6alkyl is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl.
25. The compound of claim 24 wherein C_1-C_6alkyl is methyl or iso-propyl.
26. The compound of claim 22 wherein R^{11} is a substituted or unsubstituted aryl.
27. The compound of claim 26 wherein aryl is a phenyl group.
28. The compound of claim 22 wherein R^{11} is a substituted or unsubstituted heteroaryl.
29. The compound of claim 28 wherein heteroaryl is pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, 4-azaindolyl, 5-azaindolyl, 6-azaindolyl, 7-azaindolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl,

quinazolinyl, quinoxalinyl, imidazo[1,2-a]pyridinyl, thiophenopyridinyl, and furopyridinyl.

30. The compound of claim 29 wherein heteroaryl is pyridinyl or furanyl.

31. A compound selected from (E)-N-hydroxy-3-(2-(3-methoxyphenoxy)phenyl)acrylamide; (E)-3-(2-(3-fluorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-N-hydroxy-3-(2-(pyridin-3-yloxy)phenyl)acrylamide; (E)-N-hydroxy-3-(2-(pyridin-4-yloxy)phenyl)acrylamide; (E)-N-hydroxy-3-(2-(4-methoxyphenoxy)phenyl)acrylamide; (E)-3-(2-(3-chlorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-N-hydroxy-3-(2-(m-tolyloxy)phenyl)acrylamide; (E)-N-hydroxy-3-(2-phenoxyphenyl)acrylamide; (E)-N-hydroxy-3-(2-(p-tolyloxy)phenyl)acrylamide; (E)-3-(2-(4-chlorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)phenyl)-N-hydroxyacrylamide; (S,E)-3-(2-(1-benzoylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (S,E)-3-(2-(1-acetylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (S,E)-N-hydroxy-3-(2-(1-isobutyrylpiperidin-3-yloxy)phenyl)acrylamide; (E)-3-(2-(1-(furan-2-carbonyl)piperidin-4-yloxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(1-acetylpiperidin-4-yloxy)phenyl)-N-hydroxyacrylamide; (E)-N-hydroxy-3-(2-(1-isobutyrylpiperidin-4-yloxy)phenyl)acrylamide; (E)-3-(2-(1-benzoylpiperidin-4-yloxy)phenyl)-N-hydroxyacrylamide; (E)-N-hydroxy-3-(2-(1-nicotinoylpiperidin-4-yloxy)phenyl)acrylamide; (R,E)-3-(2-(1-acetylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (S,E)-3-(2-(1-(furan-2-carbonyl)piperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (R,E)-3-(2-(1-(furan-2-carbonyl)piperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (R,E)-N-hydroxy-3-(2-(1-isobutyrylpiperidin-3-yloxy)phenyl)acrylamide; (R,E)-3-(2-(1-benzoylpiperidin-3-yloxy)phenyl)-N-hydroxyacrylamide; (R,E)-N-hydroxy-3-(2-(1-nicotinoylpiperidin-3-yloxy)phenyl)acrylamide; (S,E)-N-hydroxy-3-(2-(1-nicotinoylpiperidin-3-yloxy)phenyl)acrylamide; (E)-N-(4-(4-fluorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide; (E)-3-(5-acetamido-2-(4-fluorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(5-acetamido-2-(3-chlorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-N-(4-(3-chlorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide; (E)-N-(4-(3-fluorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide; (E)-N-(4-(3,4-dichlorophenoxy)-3-(3-(hydroxyamino)-3-oxoprop-1-enyl)phenyl)nicotinamide; (E)-3-(5-acetamido-2-(3-fluorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-5-(methylsulfonamido)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-5-(methylsulfonamido)phenyl)-N-

hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-fluorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)-5-(pyridin-3-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-fluorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)-5-(pyridin-2-ylmethylamino)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-4-(pyridin-3-ylmethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-4-(2-morpholinoethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-4-(2-(dimethylamino)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-chlorophenoxy)-4-(2-methoxyethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-fluorophenoxy)-4-(2-methoxyethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(4-(2-acetamidoethoxy)-2-(3-chlorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-fluorophenoxy)-4-(2-(dimethylamino)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3-fluorophenoxy)-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-4-(2-methoxyethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-4-(pyridin-3-ylmethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-4-(2-(dimethylamino)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(4-(2-acetamidoethoxy)-2-(4-fluorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(4-fluorophenoxy)-4-(2-(4-methylpiperazin-1-yl)ethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)-4-(2-methoxyethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(4-(2-acetamidoethoxy)-2-(3,4-dichlorophenoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)-4-(2-morpholinoethoxy)phenyl)-N-hydroxyacrylamide; (E)-3-(2-(3,4-dichlorophenoxy)-4-(pyridin-3-ylmethoxy)phenyl)-N-hydroxyacrylamide; an active metabolite, pharmaceutically acceptable solvate, pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof.

32. A pharmaceutical composition comprising (a) a compound of any of claims 1-31 or an active metabolite, pharmaceutically acceptable solvate, pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, or pharmaceutically acceptable prodrug thereof, and (b) a pharmaceutically acceptable diluent, excipient, or carrier.

33. The pharmaceutical composition of claim 32, wherein the pharmaceutical composition is formulated for intravenous injection, subcutaneous injection, oral administration, inhalation, nasal administration, topical administration, ophthalmic administration or otic administration.

34. The pharmaceutical composition of claim 32, wherein the pharmaceutical composition is a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye drop or an ear drop.

35. A method of treating T-cell lymphoma or leukemia in a mammal in need thereof, comprising administering to the mammal a pharmaceutical composition containing a therapeutically effective amount of a compound of claims 1-31.

36. The method of claim 35, further comprising administering to the mammal a second therapeutic agent, selected from among abarelix; aldesleukin; Aldesleukin; Alemtuzumab; alitretinoin; allopurinol; altretamine; amifostine; anastrozole; arsenic trioxide; asparaginase; azacitidine; bevacizumab; bexarotene; bleomycin; bortezomib; busulfan; busulfan; calusterone; capecitabine; carboplatin; carmustine; carmustine; celecoxib; cetuximab; chlorambucil; cisplatin; cladribine; clofarabine; cyclophosphamide; cytarabine; cytarabine liposomal; dacarbazine; dactinomycin; Darbepoetin alfa; dasatinib; daunorubicin liposomal; daunorubicin; daunorubicin; decitabine; denileukin; dexrazoxane; docetaxel; doxorubicin; doxorubicin liposomal; dromostanolone propionate; epirubicin; Epirubicin; Epoetin alfa; erlotinib; estramustine; etoposide phosphate; etoposide; exemestane; Filgrastim; floxuridine; fludarabine; fluorouracil; fulvestrant; gefitinib; gemcitabine; gemtuzumab ozogamicin; goserelin acetate; histrelin acetate; hydroxyurea; Ibritumomab Tiuxetan; idarubicin; ifosfamide; imatinib mesylate; interferon alfa 2a; Interferon alfa-2b; irinotecan; lenalidomide; letrozole; leucovorin; Leuprolide Acetate; levamisole; lomustine; meclorethamine, nitrogen mustard; megestrol acetate; melphalan; mercaptopurine; methotrexate; methoxsalen; mitomycin C; mitomycin C; mitotane; mitoxantrone; nandrolone phenpropionate; nelarabine; Nofetumomab; Oprelvekin; oxaliplatin; paclitaxel; paclitaxel; paclitaxel protein-bound particles; palifermin; pamidronate; panitumumab; pegademase; pegaspargase; Pegfilgrastim; pemetrexed disodium; pentostatin; pipobroman; plicamycin, mithramycin; porfimer sodium; procarbazine; quinacrine; Rasburicase; rituximab; sargramostim; Sargramostim; sorafenib; streptozocin; sunitinib maleate; tamoxifen; temozolomide; teniposide; testolactone; thalidomide; thioguanine; thiotepa; topotecan; toremifene;

tositumomab; tositumomab/I-131 tositumomab; trastuzumab; tretinoin; Uracil Mustard; valrubicin; vinblastine; vincristine; vinorelbine; vorinostat; zoledronate; and zoledronic acid.

37. A compound of any one of claims 1-31 for treating T-cell lymphoma or leukemia in a mammal.

38. Use of a compound of any one of claims 1-31 in the manufacture of a medicament for treating T-cell lymphoma or leukemia in a mammal.

39. A method of treating a disease or condition mediated by interleukin-1 beta (IL-1b) or IL-18 in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-31, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

40. The method of claim 39, wherein the disease or condition is selected from among osteoarthritis, rheumatoid arthritis, septic arthritis, gout, pseudogout, juvenile arthritis, Still's disease, Ankylosing spondylitis, systemic lupus erythematosus (SLE), Henoch-Schönlein purpura, psoriatic arthritis, reactive arthritis (Reiter's syndrome), hemochromatosis, hepatitis, Wegener's granulomatosis, Familial Mediterranean fever (FMF), HIDS (hyperimmunoglobulinemia D and periodic fever syndrome), TRAPS (TNF-alpha receptor associated periodic fever syndrome), inflammatory bowel disease, Crohn's Disease, ulcerative colitis, recurrent fever, anemia, leukocytosis, asthma, chronic obstructive pulmonary disease, and myalgia.

41. The method of claim 40, further comprising administering to the mammal a second therapeutic agent, selected from among tacrolimus, cyclosporin, rapamicin, methotrexate , cyclophosphamide, azathioprine, mercaptopurine, mycophenolate, or FTY720, prednisone, cortisone acetate, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, fludrocortisone acetate, deoxycorticosterone acetate, aldosterone, aspirin, salicylic acid, gentisic acid, choline magnesium salicylate, choline salicylate, choline magnesium salicylate, choline salicylate, magnesium salicylate, sodium salicylate, diflunisal, carprofen, fenoprofen, fenoprofen calcium, flurobiprofen, ibuprofen, ketoprofen, nabutone, ketolorac, ketorolac tromethamine, naproxen, oxaprozin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, meclofenamate, meclofenamate sodium, mefenamic acid, piroxicam, meloxicam, celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib, lumiracoxib, CS-502, JTE-522, L-745,337 and NS398, leflunomide, gold thioglucose, gold thiomalate,

aurofin, sulfasalazine, hydroxychloroquinine, minocycline, infliximab, etanercept, adalimumab, abatacept, anakinra, interferon-β, interferon-γ, interleukin-2, allergy vaccines, antihistamines, antileukotrienes, beta-agonists, theophylline, and anticholinergics.

42. Compound of any one of claims 1-31 for treating a disease or condition mediated by interleukin-1 beta (IL-1b) or IL-18 in a mammal.

43. Use of a compound of any one of claims 1-31 in the manufacture of a medicament for treating a disease or condition mediated by interleukin-1 beta (IL-1b) or IL-18 in a mammal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/070671

A. CLASSIFICATION OF SUBJECT MATTER

C07C 235/34(2006.01)i, A61K 31/16(2006.01)i, A61P 43/00(2006.01)i

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)

C07C 235/34; C07D 403/10; C07D 403/06; C07C 69/736; A23K 1/18; A01K 67/033; C07C 241/04; A61K 31/4439; A01N 37/10; A61K 31/343; C07C 243/38; C07D 249/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: cinnamic aicd hydroxyamide, histone deacetylase, cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010-0256401 A1 (C.-Y. HUANG et al.) 07 October 2010 See abstract and compounds 4a-4e, 16a-16d.	1-3,31
X	EP 2277387 A1 (NATUREWISE BIOTECH & MEDICALS CORPORATION) 26 January 2011 See abstract, compound (II) in paragraph [0048], NBM-T-BX-OS01, NBM-T-BCX-OS01, NBM-T-BCX-OS01, NBM-T-BMX-OS01, NBM-T-BtX-OS01, etc.	1-3,31
A	WO 2011-019393 A2 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE) 17 February 2011 See the whole document.	1-3,31
A	WO 2011-021209 A1 (PORTSMOUTH TECHNOLOGIES LLC) 24 February 2011 See the whole document.	1-3,31
A	WO 2011-103189 A1 (UWM RESEARCH FOUNDATION, INC.) 25 August 2011 See the whole document.	1-3,31
A	US 2011-0060009 A1 (C. A. BROOKS et al.) 10 March 2011 See the whole document.	1-3,31

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

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"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
17 April 2013 (17.04.2013)	**19 April 2013 (19.04.2013)**
Name and mailing address of the ISA/KR Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer LEE, Sun Hwa Telephone No. 82-42-481-5603

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/070671

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 35, 36, 39-41
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 35, 36, 39-41 are directed to a treatment method of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required to search under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT.

2. ☒ Claims Nos.: 5-12, 14, 15, 17, 19-30, 33, 34, 36, 40, 41
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 5, 14, 17, 19, 33, 34, 36 and 40 refer to any one of multiple dependent claims which are not drafted in accordance with the third sentence of PCT Rule 6.4(a). Claims 6-12, 15, 20-30 and 41 refer to any one of unclear claims. Thus above claims are unclear under PCT Article 6.

3. ☒ Claims Nos.: 4, 13, 16, 18, 32, 35, 37-39, 42, 43
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2012/070671

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010-0256401 A1	07.10.2010	AU 2010-201322 A1	21.10.2010
		AU 2010-201322 B2	25.08.2011
		BR PI1005131 A2	17.04.2012
		CN 101857554 A	13.10.2010
		JP 2011-020999 A	03.02.2011
		KR 10-1208760 B1	05.12.2012
		KR 10-2010-0110756 A	13.10.2010
		RU 2010112787 A	10.10.2011
		TW 201036940 A	16.10.2010
		US 2011-224294 A1	15.09.2011
		US 7994357 B2	09.08.2011
EP 2277387 A1	26.01.2011	None	
WO 2011-019393 A2	17.02.2011	WO 2011-019393 A3	16.06.2011
WO 2011-021209 A1	24.02.2011	CN 102548975 A	04.07.2012
		EP 2451790 A1	16.05.2012
		JP 2012-532861 A	20.12.2012
		US 2012-0101099 A1	26.04.2012
WO 2011-103189 A1	25.08.2011	EP 2536275 A1	26.12.2012
US 2011-0060009 A1	10.03.2011	None	

(19)中华人民共和国国家知识产权局

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代理人 王思琪 郑霞
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C07C 235/34(2006.01)
A61K 31/16(2006.01)
A61P 43/00(2006.01)

权利要求书6页 说明书91页

(54)发明名称

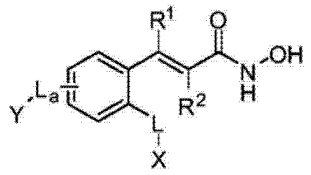
作为组蛋白脱乙酰酶8抑制剂的肉桂酸羟基酰胺

(57)摘要

本文描述了抑制组蛋白脱乙酰酶8(HDAC8)活性的化合物以及含有此类化合物的药物组合物。本文还描述了单独以及与其他化合物联合使用此类HDAC8抑制剂用于治疗将受益于HDAC8活性的抑制的疾病或状况的方法。

CN 104136410 A

1. 一种具有式 I 结构的化合物：



式 I

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

L 和 L_a 各自独立地是键、O、S、NR^3、$-NR^{10}C(=O)-R^{11}$、$S(=O)$、$S(=O)_2$、$NHS(=O)_2$、$-C_1$-C_6 亚烷基 -、$-C_2$-C_6 亚烯基 -、$-C_2$-C_6 亚炔基 -、$-C_1$-C_6 亚杂烷基 -、$-C_1$-C_6 亚烷基 -O-、$-C_1$-C_3 亚烷基 -O-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3-$、$-C_1$-C_3 亚烷基 $-NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-C(=O)NR^3-$、$-C_1$-C_3 亚烷基 $-C(=O)NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3C(=O)-$、$-C_1$-C_3 亚烷基 $-NR^3C(=O)-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -S-、$-C_1$-C_3 亚烷基 -S-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-S(=O)-$、$-C_1$-C_3 亚烷基 $-S(=O)-C_1$-C_3 亚烷基、C_1-C_6 亚烷基 $-S(=O)_2-$、$-C_1$-C_3 亚烷基 $-S(=O)_2-C_1$-C_3 亚烷基、$-C(=O)-$ 或 $-C(=O)-C_1$-C_6 亚烷基；

X 是选自芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 X 是取代的，那么 X 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

Y 是 H 或选自 C_1-C_6 烷基、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 Y 是取代的，那么 Y 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

R^{10} 是 H 或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^3 是 H、C_1-C_6 烷基、苯基或苄基；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

2. 根据权利要求 1 所述的化合物，其中 R^1 和 R^2 各自独立地是 H。

3. 根据权利要求 1 或 2 所述的化合物，其中 L 是 O 或 S。

4. 根据权利要求 1-3 中的任一项所述的化合物，其中 X 是取代或未取代的芳基。

5. 根据权利要求 4 所述的化合物，其中芳基是苯基。

6. 根据权利要求 5 所述的化合物，其中苯基是被 Cl、Br、I 或 F 中的至少一个所取代的。

7. 根据权利要求 5 所述的化合物，其中苯基是被 Cl、Br、I 或 F 中的至少两个所取代的。

8. 根据权利要求 5 所述的化合物，其中苯基是被至少一个 C_1-C_6 烷基所取代的。

9. 根据权利要求 8 所述的化合物，其中 C_1-C_6 烷基是甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

10. 根据权利要求 9 所述的化合物，其中 C_1-C_6 烷基是甲基。

11. 根据权利要求 5 所述的化合物，其中苯基是被至少一个 C_1-C_6 烷氧基所取代的。

12. 根据权利要求 11 所述的化合物，其中 C_1-C_6 烷氧基选自甲氧基或乙氧基。

13. 根据权利要求 1-3 中的任一项所述的化合物，其中 X 是取代或未取代的杂芳基。

14. 根据权利要求 13 所述的化合物，其中杂芳基是吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、4- 氮杂吲哚基、5- 氮杂吲哚基、6- 氮杂吲哚基、7- 氮杂吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、咪唑并 [1,2-a] 吡啶基、噻吩并吡啶基和呋喃并吡啶基。

15. 根据权利要求 14 所述的化合物，其中杂芳基是吡啶基。

16. 根据权利要求 1-3 中的任一项所述的化合物，其中 X 是取代或未取代的 C_3-C_{10} 环烷基。

17. 根据权利要求 16 所述的化合物，其中 C_3-C_{10} 环烷基是环丙基、环丁基、环戊基和环己基。

18. 根据权利要求 1-3 中的任一项所述的化合物，其中 X 是取代或未取代的 C_2-C_{10} 杂环烷基。

19. 根据权利要求 18 所述的化合物，其中 C_2-C_{10} 杂环烷基是喹嗪基、二氧杂环己烯基、哌啶基、吗啉基、硫代吗啉基、噻嗪基、四氢吡啶基、哌嗪基、噁嗪烷酮基、二氢吡咯基、二氢咪唑基、四氢呋喃基、四氢吡喃基、二氢噁唑基、环氧乙烷基、吡咯烷基、吡唑烷基、二氢噻吩基、咪唑烷酮基、吡咯烷酮基、二氢呋喃酮基、二氧杂环戊烷酮基、噻唑烷基、哌啶酮基、二氢吲哚基、四氢喹啉基、四氢异喹啉基和四氢噻吩基。

20. 根据权利要求 19 所述的化合物，其中 C_2-C_{10} 杂环烷基是哌啶基。

21. 根据权利要求 20 所述的化合物，其中哌啶基是被 $-CO_2R^{10}$、$-C(=O)R^{11}$ 或 $-C(=O)N(R^{10})_2$ 取代的。

22. 根据权利要求 21 所述的化合物，其中哌啶基是被 $-C(=O)R^{11}$ 取代的。

23. 根据权利要求 22 所述的化合物，其中 R^{11} 是取代或未取代的 C_1-C_6 烷基。

24. 根据权利要求 23 所述的化合物，其中 C_1-C_6 烷基是甲基、乙基、正丙基、异丙基、正

丁基、异丁基或叔丁基。

25. 根据权利要求 24 所述的化合物，其中 C_1-C_6 烷基是甲基或异丙基。

26. 根据权利要求 22 所述的化合物，其中 R^{11} 是取代或未取代的芳基。

27. 根据权利要求 26 所述的化合物，其中芳基是苯基基团。

28. 根据权利要求 22 所述的化合物，其中 R^{11} 是取代或未取代的杂芳基。

29. 根据权利要求 28 所述的化合物，其中杂芳基是吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、4- 氮杂吲哚基、5- 氮杂吲哚基、6- 氮杂吲哚基、7- 氮杂吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、咪唑并 [1,2-a] 吡啶基、噻吩并吡啶基和呋喃并吡啶基。

30. 根据权利要求 29 所述的化合物，其中杂芳基是吡啶基或呋喃基。

31. 一种化合物，其选自 (E)-N- 羟基 -3-(2-(3- 甲氧基苯氧基) 苯基) 丙烯酰胺、(E)-3-(2-(3- 氟苯氧基) 苯基)-N- 羟基丙烯酰胺、(E)-N- 羟基 -3-(2-(吡啶 -3- 基氧基) 苯基) 丙烯酰胺、(E)-N- 羟基 -3-(2-(吡啶 -4- 基氧基) 苯基) 丙烯酰胺、(E)-N- 羟基 -3-(2-(4- 甲氧基苯氧基) 苯基) 丙烯酰胺、(E)-3-(2-(3- 氯苯氧基) 苯基)-N- 羟基丙烯酰胺、(E)-3-(2-(3,4- 二氯苯氧基) 苯基)-N- 羟基丙烯酰胺、(E)-N- 羟基 -3-(2-(间甲苯氧基) 苯基) 丙烯酰胺、(E)-N- 羟基 -3-(2- 苯氧基苯基) 丙烯酰胺、(E)-N- 羟基 -3-(2-(对甲苯氧基) 苯基) 丙烯酰胺、(E)-3-(2-(4- 氯苯氧基) 苯基)-N- 羟基丙烯酰胺、(E)-3-(2-(4- 氟苯氧基) 苯基)-N- 羟基丙烯酰胺、(S, E)-3-(2-(1- 苯甲酰基哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺、(S, E)-3-(2-(1- 乙酰基哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺、(S, E)-N- 羟基 -3-(2-(1- 异丁酰基哌啶 -3- 基氧基) 苯基) 丙烯酰胺、(E)-3-(2-(1-(呋喃 -2- 羰基) 哌啶 -4- 基氧基) 苯基)-N- 羟基丙烯酰胺、(E)-3-(2-(1- 乙酰基哌啶 -4- 基氧基) 苯基)-N- 羟基丙烯酰胺、(E)-N- 羟基 -3-(2-(1- 异丁酰基哌啶 -4- 基氧基) 苯基) 丙烯酰胺、(E)-3-(2-(1- 苯甲酰基哌啶 -4- 基氧基) 苯基)-N- 羟基丙烯酰胺、(E)-N- 羟基 -3-(2-(1- 烟酰基哌啶 -4- 基氧基) 苯基) 丙烯酰胺、(R, E)-3-(2-(1- 乙酰基哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺、(S, E)-3-(2-(1-(呋喃 -2- 羰基) 哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺、(R, E)-3-(2-(1-(呋喃 -2- 羰基) 哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺、(R, E)-N- 羟基 -3-(2-(1- 异丁酰基哌啶 -3- 基氧基) 苯基) 丙烯酰胺、(R, E)-3-(2-(1- 苯甲酰基哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺、(R, E)-N- 羟基 -3-(2-(1- 烟酰基哌啶 -3- 基氧基) 苯基) 丙烯酰胺、(S, E)-N- 羟基 -3-(2-(1- 烟酰基哌啶 -3- 基氧基) 苯基) 丙烯酰胺、(E)-N-(4-(4- 氟苯氧基)-3-(3-(羟基氨基)-3- 氧代丙 -1- 烯基) 苯基) 烟酰胺、(E)-3-(5- 乙酰氨基 -2-(4- 氟苯氧基) 苯基)-N- 羟基丙烯酰胺、(E)-3-(5- 乙酰氨基 -2-(3- 氯苯氧基) 苯基)-N- 羟基丙烯酰胺、(E)-N-(4-(3- 氯苯氧基)-3-(3-(羟基氨基)-3- 氧代丙 -1- 烯基) 苯基) 烟酰胺、(E)-N-(4-(3- 氟苯氧基)-3-(3-(羟基氨基)-3- 氧代丙 -1- 烯基) 苯基) 烟酰胺、(E)-N-(4-(3,4- 二氯苯氧基)-3-(3-(羟基氨基)-3- 氧代丙 -1- 烯基) 苯基) 烟酰胺、(E)-3-(5- 乙酰氨基 -2-(3- 氟苯氧基) 苯基)-N- 羟基丙烯酰胺、(E)-3-(2-(4- 氟苯氧基)-5-(甲基磺酰胺基) 苯基)-N- 羟基丙烯酰胺、

(E)-3-(2-(3-氯苯氧基)-5-(甲基磺酰胺基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-5-(吡啶-3-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-5-(吡啶-3-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-5-(吡啶-2-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-5-(吡啶-2-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氟苯氧基)-5-(吡啶-3-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3,4-二氯苯氧基)-5-(吡啶-3-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氟苯氧基)-5-(吡啶-2-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3,4-二氯苯氧基)-5-(吡啶-2-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-4-(吡啶-3-基甲氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-4-(2-吗啉基乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-4-(2-(4-甲基哌嗪-1-基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-4-(2-(二甲基氨基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-4-(2-甲氧基乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氟苯氧基)-4-(2-甲氧基乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(4-(2-乙酰氨基乙氧基)-2-(3-氯苯氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氟苯氧基)-4-(2-(二甲基氨基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氟苯氧基)-4-(2-(4-甲基哌嗪-1-基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-4-(2-甲氧基乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-4-(吡啶-3-基甲氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-4-(2-(二甲基氨基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(4-(2-乙酰氨基乙氧基)-2-(4-氟苯氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-4-(2-(4-甲基哌嗪-1-基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3,4-二氯苯氧基)-4-(2-甲氧基乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(4-(2-乙酰氨基乙氧基)-2-(3,4-二氯苯氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3,4-二氯苯氧基)-4-(2-吗啉基乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3,4-二氯苯氧基)-4-(吡啶-3-基甲氧基)苯基)-N-羟基丙烯酰胺;其活性代谢物、药学上可接受的溶剂化物、药学上可接受的盐、药学上可接受的N-氧化物或药学上可接受的前药。

32. 一种药物组合物,其包含(a)根据权利要求1-31中的任一项所述的化合物或其活性代谢物、药学上可接受的溶剂化物、药学上可接受的盐、药学上可接受的N-氧化物或药学上可接受的前药,以及(b)药学上可接受的稀释剂、赋形剂或载体。

33. 根据权利要求32所述的药物组合物,其中所述药物组合物配制为用于静脉内注射、皮下注射、口服给药、吸入、经鼻给药、局部给药、经眼给药或经耳给药。

34. 根据权利要求32所述的药物组合物,其中所述药物组合物是片剂、丸剂、胶囊、液体、吸入剂、喷鼻剂、栓剂、悬浮液、凝胶、胶体、分散体、悬浮液、溶液、乳剂、软膏、洗剂、滴眼剂或滴耳剂。

35. 一种在有需要的哺乳动物中治疗T细胞淋巴瘤或白血病的方法,其包括对该哺乳动物施用含有治疗有效量的权利要求1-31的化合物的药物组合物。

36. 根据权利要求35所述的方法,其进一步包括向哺乳动物施用第二治疗剂,该第二治疗剂选自阿巴瑞克、阿地白介素、阿地白介素、阿仑珠单抗、阿利维a酸、别嘌醇、六甲蜜

胺、氨磷汀、阿那曲唑、三氧化二砷、门冬酰胺酶、阿扎胞苷、贝伐珠单抗、贝沙罗汀、博来霉素、硼替佐米、白消安、白消安、卡芦睾酮、卡培他滨、卡铂、卡莫司汀、卡莫司汀、塞来昔布、西妥昔单抗、苯丁酸氮芥、顺铂、克拉屈滨、氯法拉滨、环磷酰胺、阿糖胞苷、阿糖胞苷脂质体、达卡巴嗪、更生霉素、达依泊汀 α、达沙替尼、柔红霉素脂质体、柔红霉素、柔红霉素、地西他滨、地尼白介素、右雷佐生、多西他赛、多柔比星、多柔比星脂质体、丙酸屈他雄酮、表柔比星、表柔比星、依泊汀 α、厄洛替尼、雌莫司汀、磷酸依托泊苷、依托泊苷、依西美坦、非格司亭、氟尿苷、氟达拉滨、氟尿嘧啶、氟维司群、吉非替尼、吉西他滨、吉妥珠单抗奥佐米星、醋酸戈舍瑞林、醋酸组氨瑞林、羟基脲、替伊莫单抗、伊达比星、异环磷酰胺、甲磺酸伊马替尼、干扰素 α 2a、干扰素 α-2b、伊立替康、来那度胺、来曲唑、亚叶酸、醋酸亮丙瑞林、左旋咪唑、洛莫司汀、二氯甲基二乙胺、氮芥、醋酸甲地孕酮、美法仑、巯嘌呤、氨甲蝶呤、甲氧沙林、丝裂霉素 C、丝裂霉素 C、米托坦、米托蒽醌、苯丙酸诺龙、奈拉滨、诺非单抗、奥普瑞白介素、奥沙利铂、紫杉醇、紫杉醇、紫杉醇蛋白质结合颗粒、帕利夫明、帕米膦酸盐、帕尼单抗、培加酶、培门冬酶、培非司亭、培美曲塞二钠、喷司他丁、哌泊溴烷、普卡霉素，光辉霉素、卟吩姆钠、丙卡巴肼、奎纳克林、拉布立酶、利妥昔单抗、沙格司亭、沙格司亭、索拉非尼、链佐星、马来酸舒尼替尼、他莫昔芬、替莫唑胺、替尼泊苷、睾内酯、沙利度胺、硫鸟嘌呤、噻替哌、托泊替康、托瑞米芬、托西莫单抗、托西莫单抗 /I-131 托西莫单抗、曲妥珠单抗、维甲酸、尿嘧啶氮芥、戊柔比星、长春碱、长春新碱、长春瑞滨、伏林司他、唑来膦酸盐和唑来膦酸。

37. 根据权利要求 1-31 中的任一项所述的化合物，其用于治疗哺乳动物中的 T 细胞淋巴瘤或白血病。

38. 根据权利要求 1-31 中任一项所述的化合物在制备用于治疗哺乳动物 T 细胞淋巴瘤或白血病的药物中的用途。

39. 一种治疗哺乳动物中由白介素 -1 β (IL-1b) 或 IL-18 介导的疾病或状况的方法，其包括向该哺乳动物施用治疗有效量的权利要求 1-31 中任一项所述的化合物，或其药学上可接受的盐、药学上可接受的 N- 氧化物、药学活性代谢物、药学上可接受的前药或药学上可接受的溶剂化物。

40. 根据权利要求 39 所述的方法，其中所述疾病或状况是选自骨关节炎、类风湿性关节炎、脓毒性关节炎、痛风、假痛风、幼年型关节炎、斯蒂尔病、强直性脊柱炎、系统性红斑狼疮 (SLE)、Henoch- Schönlein 紫癜、牛皮癣关节炎、反应性关节炎（莱特尔综合征）、血色素沉着病、肝炎、韦格纳肉芽肿病、家族性地中海热 (FMF)、HIDS（高免疫球蛋白血症 D 和周期性发热综合征）、TRAPS(TNF-α 受体相关的周期性发热综合征）、炎性肠病、克罗恩病、溃疡性结肠炎、回归热、贫血、白细胞增多、哮喘、慢性阻塞性肺病及肌痛。

41. 根据权利要求 40 所述的方法，其进一步包括向哺乳动物施用第二治疗剂，该第二治疗剂选自他克莫司、环孢菌素、雷帕霉素、氨甲蝶呤、环磷酰胺、硫唑嘌呤、硫嘌呤、麦考酚酯或 FTY720、强的松、醋酸可的松、泼尼松龙、甲泼尼龙、地塞米松、倍他米松、曲安西龙、倍氯米松、醋酸氟氢可的松、醋酸脱氧皮质酮、醛甾酮、阿司匹林、水杨酸、龙胆酸、胆碱水杨酸镁、水杨酸胆碱、胆碱水杨酸镁、水杨酸胆碱、水杨酸镁、水杨酸钠、二氟尼柳、卡洛芬、非诺洛芬、非诺洛芬钙、氟比洛芬、布洛芬、酮洛芬、纳布美通、酮咯酸、酮咯酸氨丁三醇、萘普生、奥沙普秦、双氯芬酸、依托度酸、吲哚美辛、舒林酸、托美丁、甲氯芬那酸盐、甲氯芬那酸钠、甲芬那酸、吡罗昔康、美洛昔康、塞来昔布、罗非昔布、伐地考昔、帕瑞考昔、依托考昔、芦米

考昔、CS-502、JTE-522、L-745,337 和 NS398、来氟米特、硫化葡糖金、硫代苹果酸金、金诺分、柳氮磺胺吡啶、羟基氯喹、米诺环素、英利昔单抗、依那西普、阿达木单抗、阿巴西普、阿那白滞素、干扰素 -β、干扰素 -γ、白介素 -2、变态反应疫苗、抗组胺药、抗白三烯、β-激动剂、茶碱及抗胆碱能药。

42. 根据权利要求 1-31 中的任一项所述的化合物,其用于治疗哺乳动物中由白介素 -1β (IL-1b) 或 IL-18 介导的疾病或状况。

43. 根据权利要求 1-31 中任一项所述的化合物在制备用于治疗哺乳动物中由白介素 -1β (IL-1b) 或 IL-18 介导的疾病或状况的药物中的用途。

作为组蛋白脱乙酰酶 8 抑制剂的肉桂酸羟基酰胺

相关申请

[0001] 本申请要求 2011 年 12 月 29 日提交的、名称为“CINNAMIC ACID HYDROXYAMIDES AS INHIBITORS OF HISTONE DEACETYLASE 8”的美国临时专利申请号 61/581,459 的权益，该临时申请通过引用全部并入本文。

技术领域

[0002] 本发明描述了化合物、制备此类化合物的方法、包含此类化合物的药物组合物和药物，以及利用此类化合物抑制组蛋白脱乙酰酶 8 的活性的方法。

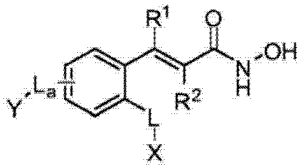
背景技术

[0003] 组蛋白脱乙酰酶 (HDAC) 催化乙酰基从组蛋白上的脱除，组蛋白是在核小体中组织和调节染色质结构的蛋白质。染色质结合的组蛋白的 HDAC 介导的脱乙酰作用调控整个基因组中多种基因的表达。重要的是，HDAC 已经与癌症以及其他健康状况相关联。迄今为止，已经描述了十一种主要的 HDAC 同种型 (HDAC 1-11)。HDAC 被分成两类。I 类 HDAC 包括 HDAC1、HDAC2、HDAC3、HDAC8 和 HDAC11。II 类 HDAC 包括 HDAC4、HDAC5、HDAC6、HDAC7、HDAC9 和 HDAC10。具有同种型选择性的小分子 HDAC 抑制剂作为具有减弱的毒性的治疗剂和作为用于探索 HDAC 同种型生物学的工具是有用的。

发明内容

[0004] 在一方面，本发明提供了取代的肉桂酸羟基酰胺化合物和其他 HDAC8 抑制剂、其药学上可接受的盐、药学上可接受的 N- 氧化物、药学活性代谢物、药学上可接受的前药以及药学上可接受的溶剂化物。在一些实施方案中，本文所述的化合物抑制 HDAC8 的活性。在一些实施方案中，本文所述的化合物用于治疗其中对 HDAC8 活性的抑制提供益处的哺乳动物。本文所述的化合物是 HDAC8 抑制剂。

[0005] 在一方面，本文描述了具有式 (I) 结构的化合物：



式(I)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

L 和 L_a 各自独立地是键、O、S、NR^3、$-NR^{10}C(=O)-R^{11}$、$S(=O)$、$S(=O)_2$、$NHS(=O)_2$、$-C_1$-C_6 亚烷基 -、$-C_2$-C_6 亚烯基 -、$-C_2$-C_6 亚炔基 -、$-C_1$-C_6 亚杂烷基 -、$-C_1$-C_6 亚烷基 -O-、$-C_1$-C_3 亚烷基 -O-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3-$、$-C_1$-C_3 亚烷基 $-NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-C(=O)NR^3-$、$-C_1$-C_3 亚烷基 $-C(=O)NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷

基 $-NR^3C(=O)-$、$-C_1-C_3$ 亚烷基 $-NR^3C(=O)-C_1-C_3$ 亚烷基 -、$-C_1-C_6$ 亚烷基 -S-、$-C_1-C_3$ 亚烷基 $-S-C_1-C_3$ 亚烷基 -、$-C_1-C_6$ 亚烷基 $-S(=O)-$、$-C_1-C_3$ 亚烷基 $-S(=O)-C_1-C_3$ 亚烷基、$-C_1-C_6$ 亚烷基 $-S(=O)_2-$、$-C_1-C_3$ 亚烷基 $-S(=O)_2-C_1-C_3$ 亚烷基、$-C(=O)-$ 或 $-C(=O)-C_1-C_6$ 亚烷基；

X 是选自芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 X 是取代的，那么 X 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1-C_2$ 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基及取代或未取代的杂芳基；

Y 是 H 或选自 C_1-C_6 烷基、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 Y 是取代的，那么 Y 被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1-C_2$ 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基及取代或未取代的杂芳基；

R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^3 是 H、C_1-C_6 烷基、苯基或苄基；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0006] 对于任何和所有的实施方案，取代基选自所列出的备选基团的子集。例如，在一些实施方案中，R^1 是氢或 C_1-C_6 烷基。在一些其他实施方案中，R^2 是氢或 C_1-C_6 烷基。在其他实施方案中，R^1 和 R^2 各自是氢。

[0007] 在一个实施方案中，L 是 O 或 S。

[0008] 在另一个实施方案中，X 是取代或未取代的芳基。在又一个其他实施方案中，芳基是苯基。

[0009] 在另一个实施方案中，苯基被 Cl、Br、I 或 F 中的至少一个所取代。在又一个实施方案中，苯基被 Cl、B_r、I 或 F 中的至少两个所取代。

[0010] 在一个实施方案中，苯基被至少一个 C_1-C_6 烷基所取代。在另一个实施方案中，C_1-C_6 烷基是甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

[0011] 在又一个其他实施方案中，C_1-C_6 烷基是甲基。

[0012] 在另一个实施方案中，苯基被至少一个 C_1-C_6 烷氧基所取代。在另一个实施方案中，C_1-C_6 烷氧基选自甲氧基或乙氧基。

[0013] 在一个实施方案中，X 是取代或未取代的杂芳基。在另一个实施方案中，杂芳基是吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、4- 氮杂吲哚基、5- 氮杂吲哚基、6- 氮杂吲哚基、7- 氮杂吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、咪唑并 [1,2-a] 吡啶基、噻吩并吡啶基和呋喃并吡啶基。

[0014] 在又一个实施方案中，杂芳基是吡啶基。

[0015] 在另一个实施方案中，X 是取代或未取代的 C_3-C_{10} 环烷基。在又一个实施方案中，C_3-C_{10} 环烷基是环丙基、环丁基、环戊基和环己基。

[0016] 在一个实施方案中，X 是取代或未取代的 C_2-C_{10} 杂环烷基。

[0017] 在另一个实施方案中，C_2-C_{10} 杂环烷基是喹嗪基、二氧杂环己烯基、哌啶基、吗啉基、硫代吗啉基、噻嗪基、四氢吡啶基、哌嗪基、噁嗪烷酮基 (oxazinanonyl)、二氢吡咯基、二氢咪唑基、四氢呋喃基、四氢吡喃基、二氢噁唑基、环氧乙烷基、吡咯烷基、吡唑烷基、二氢噻吩基、咪唑烷酮基、吡咯烷酮基、二氢呋喃酮基 (dihydrofuranonyl)、二氧杂环戊烷酮基 (dioxolanonyl)、噻唑烷基、哌啶酮基 (piperidinonyl)、二氢吲哚基、四氢喹啉基、四氢异喹啉基和四氢噻吩基。在又一个实施方案中，C_2-C_{10} 杂环烷基是哌啶基。在另一个实施方案中，哌啶基被 $-CO_2R^{10}$、$-C(=O)R^{11}$ 或 $-C(=O)N(R^{10})_2$ 所取代。在又一个实施方案中，哌啶基被 $-C(=O)R^{11}$ 取代。

[0018] 在一个实施方案中，R11 是取代或未取代的 C_1-C_6 烷基。在另一个实施方案中，C_1-C_6 烷基是甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。

[0019] 在又一个实施方案中，C_1-C_6 烷基是甲基或异丙基。

[0020] 在另一个实施方案中，R^{11} 是取代或未取代的芳基。在又一个实施方案中，芳基是苯基。

[0021] 在一个实施方案中，R11 是取代或未取代的杂芳基。在另一个实施方案中，杂芳基是吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、4- 氮杂吲哚基、5- 氮杂吲哚基、6- 氮杂吲哚基、7- 氮杂吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、咪唑并 [1,2-a] 吡啶基、噻吩并吡啶基和呋喃并吡啶基。在又一个实施方案中，杂芳基是吡啶基或呋喃基。

[0022] 在一个方面是选自以下的化合物：(E)-N- 羟基 -3-(2-(3- 甲氧基苯氧基）苯基）丙烯酰胺、(E)-3-(2-(3- 氟苯氧基）苯基)-N- 羟基丙烯酰胺、(E)-N- 羟基 -3-(2-(吡啶 -3- 基氧基）苯基）丙烯酰胺、(E)-N- 羟基 -3-(2-(吡啶 -4- 基氧基）苯基）丙烯酰胺、(E)-N- 羟基 -3-(2-(4- 甲氧基苯氧基）苯基）丙烯酰胺、(E)-3-(2-(3- 氯苯氧基）苯基)-N- 羟基丙烯酰胺、(E)-3-(2-(3,4- 二氯苯氧基）苯基)-N- 羟基丙烯酰胺、

(E)-N-羟基-3-(2-(间甲苯氧基)苯基)丙烯酰胺、(E)-N-羟基-3-(2-苯氧基苯基)丙烯酰胺、(E)-N-羟基-3-(2-(对甲苯氧基)苯基)丙烯酰胺、(E)-3-(2-(4-氯苯氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)苯基)-N-羟基丙烯酰胺、(S,E)-3-(2-(1-苯甲酰基哌啶-3-基氧基)苯基)-N-羟基丙烯酰胺、(S,E)-3-(2-(1-乙酰基哌啶-3-基氧基)苯基)-N-羟基丙烯酰胺、(S,E)-N-羟基-3-(2-(1-异丁酰基哌啶-3-基氧基)苯基)丙烯酰胺、(E)-3-(2-(1-(呋喃-2-羰基)哌啶-4-基氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(1-乙酰基哌啶-4-基氧基)苯基)-N-羟基丙烯酰胺、(E)-N-羟基-3-(2-(1-异丁酰基哌啶-4-基氧基)苯基)丙烯酰胺、(E)-3-(2-(1-苯甲酰基哌啶-4-基氧基)苯基)-N-羟基丙烯酰胺、(E)-N-羟基-3-(2-(1-烟酰基哌啶-4-基氧基)苯基)丙烯酰胺、(R,E)-3-(2-(1-乙酰基哌啶-3-基氧基)苯基)-N-羟基丙烯酰胺、(S,E)-3-(2-(1-(呋喃-2-羰基)哌啶-3-基氧基)苯基)-N-羟基丙烯酰胺、(R,E)-3-(2-(1-(呋喃-2-羰基)哌啶-3-基氧基)苯基)-N-羟基丙烯酰胺、(R,E)-N-羟基-3-(2-(1-异丁酰基哌啶-3-基氧基)苯基)丙烯酰胺、(R,E)-3-(2-(1-苯甲酰基哌啶-3-基氧基)苯基)-N-羟基丙烯酰胺、(R,E)-N-羟基-3-(2-(1-烟酰基哌啶-3-基氧基)苯基)丙烯酰胺、(S,E)-N-羟基-3-(2-(1-烟酰基哌啶-3-基氧基)苯基)丙烯酰胺、(E)-N-(4-(4-氟苯氧基)-3-(3-(羟基氨基)-3-氧代丙-1-烯基)苯基)烟酰胺、(E)-3-(5-乙酰氨基-2-(4-氟苯氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(5-乙酰氨基-2-(3-氯苯氧基)苯基)-N-羟基丙烯酰胺、(E)-N-(4-(3-氯苯氧基)-3-(3-(羟基氨基)-3-氧代丙-1-烯基)苯基)烟酰胺、(E)-N-(4-(3-氟苯氧基)-3-(3-(羟基氨基)-3-氧代丙-1-烯基)苯基)烟酰胺、(E)-N-(4-(3,4-二氯苯氧基)-3-(3-(羟基氨基)-3-氧代丙-1-烯基)苯基)烟酰胺、(E)-3-(5-乙酰氨基-2-(3-氟苯氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-5-(甲基磺酰胺基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-5-(甲基磺酰胺基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-5-(吡啶-3-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-5-(吡啶-3-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-5-(吡啶-2-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-5-(吡啶-2-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氟苯氧基)-5-(吡啶-3-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3,4-二氯苯氧基)-5-(吡啶-3-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氟苯氧基)-5-(吡啶-2-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3,4-二氯苯氧基)-5-(吡啶-2-基甲基氨基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-4-(吡啶-3-基甲氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-4-(2-吗啉基乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-4-(2-(4-甲基哌嗪-1-基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-4-(2-(二甲氨基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氯苯氧基)-4-(2-甲氧基乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氟苯氧基)-4-(2-甲氧基乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(4-(2-乙酰氨基乙氧基)-2-(3-氯苯氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氟苯氧基)-4-(2-(二甲基氨基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3-氟苯氧基)-4-(2-(4-甲基哌嗪-1-基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-4-(2-甲氧基

乙氧基）苯基）-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-4-(吡啶-3-基甲氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-4-(2-(二甲基氨基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(4-(2-乙酰氨基乙氧基)-2-(4-氟苯氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(4-氟苯氧基)-4-(2-(4-甲基哌嗪-1-基)乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3,4-二氯苯氧基)-4-(2-甲氧基乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(4-(2-乙酰氨基乙氧基)-2-(3,4-二氯苯氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3,4-二氯苯氧基)-4-(2-吗啉基乙氧基)苯基)-N-羟基丙烯酰胺、(E)-3-(2-(3,4-二氯苯氧基)-4-(吡啶-3-基甲氧基)苯基)-N-羟基丙烯酰胺；其活性代谢物、药学上可接受的溶剂化物、药学上可接受的盐、药学上可接受的N-氧化物或药学上可接受的前药。

[0023] 本文进一步公开了药物组合物，其包含式(I)、(II)、(III)、(IIIa)、(IV)、(IVa)、(IVb)或(IVc)的化合物或其活性代谢物、药学上可接受的溶剂化物、药学上可接受的盐、药学上可接受的N-氧化物或药学上可接受的前药，以及药学上可接受的稀释剂、赋形剂或载体。在一些实施方案中，药物组合物配制为用于静脉内注射、皮下注射、口服给药、吸入、经鼻给药、局部给药、经眼给药或经耳给药。在一些实施方案中，药物组合物配置成片剂、丸剂、胶囊、液体、吸入剂、喷鼻剂、栓剂、悬浮液、凝胶、胶体、分散体、悬浮液、溶液、乳剂、软膏、洗涤剂、滴眼剂或滴耳剂。

[0024] 此外，本文公开了药物组合物，其包含本文所述的HDAC8抑制剂化合物或其药学上可接受的盐、药学上可接受的N-氧化物或药学上可接受的前药，以及药学上可接受的稀释剂、赋形剂或载体。在一些实施方案中，药物组合物配制为用于静脉注射、皮下注射、口服给药、吸入、鼻部给药、局部给药、眼部给药或耳部给药。在一些实施方案中，药物组合物配置成片剂、丸剂、胶囊、液体、吸入剂、喷鼻剂、栓剂、悬浮液、凝胶、胶剂、分散体、悬浮液、溶液、乳化剂、药膏、洗涤剂、滴眼剂或滴耳剂。

[0025] 在某些实施方案中，本文公开了治疗哺乳动物中的T细胞淋巴瘤或白血病的方法，其包括施用本文所述的HDAC8抑制剂化合物。在一个方面，所述哺乳动物是人类。在一些实施方案中，本文所述的化合物经口服给药。

[0026] 在一个方面是本文所述的HDAC8抑制剂化合物在治疗哺乳动物的T细胞淋巴瘤或白血病中的用途。在一个方面，所述哺乳动物是人类。在一些实施方案中，本文所述的化合物经口服给药。

[0027] 在一个方面是本文所述的HDAC8抑制剂化化合物在制备用于治疗哺乳动物的T细胞淋巴瘤或白血病的药物中的用途。在一个方面，所述哺乳动物是人类。在一些实施方案中，本文所述的化合物经口服给药。

[0028] 本文还描述了在有需要的哺乳动物中治疗由白介素-1β(IL-1b)或IL-18介导的疾病或状况的方法，其包括对哺乳动物施用治疗有效量的本文所述的HDAC8抑制剂化合物或其药学上可接受的盐、药学上可接受的N-氧化物、药学活性代谢物、药学上可接受的前药或药学上可接受的前药。在一个方面，所述疾病或状况选自骨关节炎、类风湿性关节炎、脓毒性关节炎、痛风、假痛风、幼年型关节炎、斯蒂尔病(Still's disease)、强直性脊柱炎、系统性红斑狼疮(SLE)、Henoch-Schönlein紫癜、牛皮癣关节炎、反应性关节炎（莱特尔综合征）、血色素沉着病、肝炎、韦格纳肉芽肿病、家族性地中海热(FMF)、HIDS（高免疫球蛋白

血症 D 和周期性发热综合征）、TRAPS(TNF-α 受体相关的周期性发热综合征）、炎性肠病、克罗恩病、溃疡性结肠炎、回归热、贫血、白细胞增多、哮喘、慢性阻塞性肺病及肌痛。在一个方面，所述方法进一步包括对哺乳动物施用第二治疗剂，该第二治疗剂选自他克莫司、环孢菌素、雷帕霉素 (rapamicin)、氨甲蝶呤、环磷酰胺、硫唑嘌呤、硫嘌呤、麦考酚酯或 FTY720、强的松、醋酸可的松、泼尼松龙、甲泼尼龙、地塞米松、倍他米松、曲安西龙、倍氯米松、醋酸氟氢可的松、醋酸脱氧皮质酮、醛甾酮、阿司匹林、水杨酸、龙胆酸、胆碱水杨酸镁、水杨酸胆碱、胆碱水杨酸镁、水杨酸胆碱、水杨酸镁、水杨酸钠、二氟尼柳、卡洛芬、非诺洛芬、非诺洛芬钙、氟比洛芬、布洛芬、酮洛芬、纳布美通 (nabutone)、酮咯酸 (ketolorac)、酮咯酸氨丁三醇、萘普生、奥沙普秦、双氯芬酸、依托度酸、吲哚美辛、舒林酸、托美丁、甲氯芬那酸盐、甲氯芬那酸钠、甲芬那酸、吡罗昔康、美洛昔康、塞来昔布、罗非昔布、伐地考昔、帕瑞考昔、依托考昔、芦米考昔、CS-502、JTE-522、L-745，337 和 NS398、来氟米特、硫化葡糖金、硫代苹果酸金、金诺分 (aurofin)、柳氮磺胺吡啶、羟基氯喹、米诺环素、英利昔单抗、依那西普、阿达木单抗、阿巴西普、阿那白滞素、干扰素 -β、干扰素 -γ、白介素 -2、变态反应疫苗、抗组胺药、抗白三烯、β- 激动剂、茶碱及抗胆碱能药。在一个方面，所述哺乳动物是人类。在一些实施方案中，本文所述的化合物经口服给药。

[0029] 在一个方面，本文所述的 HDAC8 抑制剂化合物用于治疗哺乳动物中由白介素 -1β (IL-1b) 或 IL-18 介导的疾病或状况。在一个方面，所述疾病或状况选自骨关节炎、类风湿性关节炎、脓毒性关节炎、痛风、假痛风、幼年型关节炎、斯蒂尔病、强直性脊柱炎、系统性红斑狼疮 (SLE)、Henoch- Schönlein 紫癜、牛皮癣关节炎、反应性关节炎（莱特尔综合征）、血色素沉着病、肝炎、韦格纳肉芽肿病、家族性地中海热 (FMF)、HIDS（高免疫球蛋白血症 D 和周期性发热综合征）、TRAPS(TNF-α 受体相关的周期性发热综合征）、炎性肠病、克罗恩病、溃疡性结肠炎、回归热、贫血、白细胞增多、哮喘、慢性阻塞性肺病及肌痛。在另一方面，本文所述的 HDAC8 抑制剂化合物与第二治疗剂联合使用，该第二治疗剂选自他克莫司、环孢菌素、雷帕霉素、氨甲蝶呤、环磷酰胺、硫唑嘌呤、硫嘌呤、麦考酚酯或 FTY720、强的松、醋酸可的松、泼尼松龙、甲泼尼龙、地塞米松、倍他米松、曲安西龙、倍氯米松、醋酸氟氢可的松、醋酸脱氧皮质酮、醛甾酮、阿司匹林、水杨酸、龙胆酸、胆碱水杨酸镁、水杨酸胆碱、胆碱水杨酸镁、水杨酸胆碱、水杨酸镁、水杨酸钠、二氟尼柳、卡洛芬、非诺洛芬、非诺洛芬钙、氟比洛芬、布洛芬、酮洛芬、纳布美通、酮咯酸、酮咯酸氨丁三醇、萘普生、奥沙普秦、双氯芬酸、依托度酸、吲哚美辛、舒林酸、托美丁、甲氯芬那酸盐、甲氯芬那酸钠、甲芬那酸、吡罗昔康、美洛昔康、塞来昔布、罗非昔布、伐地考昔、帕瑞考昔、依托考昔、芦米考昔、CS-502、JTE-522、L-745，337 和 NS398、来氟米特、硫化葡糖金、硫代苹果酸金、金诺分、柳氮磺胺吡啶、羟基氯喹、米诺环素、英利昔单抗、依那西普、阿达木单抗、阿巴西普、阿那白滞素、干扰素 -β、干扰素 -γ、白介素 -2、变态反应疫苗、抗组胺药、抗白三烯、β- 激动剂、茶碱及抗胆碱能药。在一个方面，所述哺乳动物是人类。在一些实施方案中，本文所述的化合物经口服给药。

[0030] 在一个方面是本文所述的 HDAC8 抑制剂化化合物在制备用于治疗哺乳动物中由白介素 -1β (IL-1b) 或 IL-18 介导的疾病或状况的药物中的用途。在一个方面，所述哺乳动物是人类。在一些实施方案中，本文所述的化合物经口服给药。

[0031] 在任何涉及到使用 HDAC8 抑制剂化合物进行治疗的上述实施方案中，是除施用

HDAC8 抑制剂化合物外还包括施用至少一种另外的药剂的进一步的实施方案。各种药剂以任何顺序施用，包括同时施用。

[0032] 在一些实施方案中，本文所述的化合物用于抑制 HDAC8 的活性或用于治疗将会受益于对 HDAC8 活性的抑制的疾病或状况。

[0033] 在一些实施方案中，本文所述的化合物用于配制抑制 HDAC8 活性的药物。

[0034] 提供了制品，其包括包装材料，在包装材料内的本文所述的 HDAC8 抑制剂化合物，和标签，该标签指示该化合物或组合物或其药学上可接受的盐、药学上可接受的 N- 氧化物、前药或药学上可接受的溶剂化物用于抑制 HDAC8 的活性，或用于治疗、预防或改善将会受益于对 HDAC 活性的抑制的疾病或状况的一种或多种症状。

[0035] 在此描述的方法、化合物和组合物的其他目标、特征和优点根据以下详细描述将是显而易见的。然而，应当理解，该详细描述和具体实施例在表明具体实施方案时仅以说明方式给出，因为根据该详细描述，在本公开内容的精神和范围内的各种变化和修改将会变得显而易见。

发明详述

[0036] 通过乙酰化作用和脱乙酰作用的组蛋白蛋白质的共价修饰是染色质结构的重要决定因素和基因表达的调控因素。组蛋白的乙酰化作用发生在靠近这些蛋白质 N 末端的赖氨酸残基上。与组蛋白蛋白质和 DNA 的其他修饰一起，组蛋白的乙酰化状态决定染色质是处于凝缩的转录沉默状态还是处于更易接近细胞的转录机构的形式。总之，组蛋白蛋白质的超乙酰化与基因的转录激活相关。稳态组蛋白乙酰化水平源于组蛋白乙酰转移酶 (HAT) 与组蛋白脱乙酰酶 (HDAC) 的相反作用。

[0037] 组蛋白脱乙酰酶 (HDAC) 催化乙酰基从靠近组蛋白 N 末端的赖氨酸 ε- 氨基上的脱除。该反应促进染色质的凝缩，导致转录的抑制。

[0038] HDAC 抑制剂 (HDI) 以细胞特异性和基因特异性的方式正向或负向地改变基因表达。HDI 增加乙酰化的组蛋白的累积，直接影响染色质结构，从而影响核小体与基因启动子元件的关系。

[0039] 组蛋白脱乙酰酶 (HDAC) 通过组蛋白蛋白质上的乙酰化赖氨酸残基的脱乙酰化来调节基因表达。它们作为多蛋白质辅阻遏物复合物的一部分在生物系统中起作用。组蛋白脱乙酰酶已被分成三类。I 类和 II 类组蛋白脱乙酰酶 (HDAC) 是含锌的水解酶。蛋白质划分成 I 类和 II 类是基于蛋白质大小、序列相似性以及蛋白质结构域的组织化。

[0040] I 类的成员与酵母 RPD3 基因产物相关。I 类 HDAC 包括 :HDAC1、HDAC2、HDAC3、HDAC8、HDAC11。

[0041] HDAC8 是 377 个残基的 42kDa 蛋白质，定位于众多组织以及几种人类肿瘤细胞系的细胞核。GenBank 登录号 NP 060956 ;Buggy, J.J. 等，Biochem.J.,350(Pt 1), 199-205(2000) 描述了全长 HDAC8 的野生型形式。用四种不同的结合的异羟肟酸盐抑制剂解析了 HDAC8 的结构 (Somoza 等，Structure,2004,12,1325)。

[0042] II 类是酵母 HDA1 蛋白质的同源物，且包括 :HDAC4、HDAC5、HDAC6、HDAC7、HDAC9、HDAC10。

[0043] II 类 HDAC 已进一步细分成 IIa 类 (HDAC 4、5、7 和 9) 和 IIb 类 (HDAC 6 和 10)。

[0044] 第三类脱乙酰酶由 Sir2 酶家族的成员组成。这些酶具有组蛋白脱乙酰酶活性但

是在结构和进化上与 I 类和 II 类蛋白质无关。它们是（烟酰胺腺嘌呤二核苷酸）NAD 依赖性的，并且与 I 类 HDAC 和 II 类 HDAC 不同，它们不包含催化性锌位点。

[0045] 在细胞中，HDAC 蛋白质作为多成分阻遏物复合物的一部分而被募集。已经对数种含有 HDAC 的复合物进行了表征，其包括 N-CoR/SMRT、Sin3、NuRD 和 CoREST 复合物。在这些复合物内，HDAC1 和 HDAC2 通常与 mSin3、Mi-2 或 CoREST 蛋白质相互作用。已经表明，HDAC3 和 IIa 类 HDAC 与 SMRT 和相关的 N-CoR 蛋白质相互作用。已经表明，作为调节转录的手段，大量转录因子与一种辅阻遏物复合物结合。DNA 结合蛋白质对 HDAC 的募集允许针对染色质的特定区域进行组蛋白脱乙酰化，以便促进靶向转录抑制。

[0046] HDAC 因其参与调节细胞周期进程和控制中所涉及的基因而成为有希望的治疗靶点。已经表明，HDAC 的抑制下调基因，包括 p21WAF/CIP1、p27、p53 和细胞周期蛋白 E，并上调诸如细胞周期蛋白 A 和细胞周期蛋白 D 等基因。在使用 HDAC 抑制剂治疗后已经观察到在多种癌细胞系中的生长抑制，并且体内研究表明，一些此类抑制剂对减缓肿瘤生长是有效的。各种 HDAC 同工酶的生物活性取决于该酶的内在活性与辅因子结合对反应性和底物识别的影响的结合 (Schultz 等，Biochemistry，2004，43，11083-11091)。

[0047] 非选择性 HDAC 抑制剂以同等效力抑制大多数（如果不是所有的）HDAC 的脱乙酰酶活性。SAHA（非选择性 HDAC 抑制剂）的抗癌作用的机理尚未完全了解，可能是由于改变的基因表达和改变的调节细胞增殖和细胞死亡途径的蛋白质功能两者。诸如 SAHA 等非选择性 HDAC 抑制剂诱导乙酰化的组蛋白蛋白质和非组蛋白蛋白质的累积。乙酰化的非组蛋白蛋白质包括但不限于：

[0048] Bcl-6（癌蛋白质）、LEF/TCF（淋巴增强因子）、P53（肿瘤抑制蛋白）；Ku70（具有包括 DNA 修复在内的多种功能的自身抗原）、H1F-1α（血管发生）、GATA-1（转录因子）、WRN(Werner 解旋酶）、E2F-1（转录因子）、Smad7（转录因子）、Rb（肿瘤抑制蛋白）、TFIIF（转录机构）、c-Jun（转录因子）、α-微管蛋白（结构蛋白质）、HMGI(Y)（染色质结构）、ACTR（核受体辅激活蛋白）、雄激素受体（信号转导）、EKLF（红细胞 kruppel 样因子）、YY-1（转录因子）、NF-κB(RelA)（转录因子）、MyoD（转录因子）、输入蛋白 a7（核孔蛋白质）、Hsp90（侣伴蛋白质）、TFIIE（转录机构）、b-联蛋白（信号转导）、TFJB（转录因子）。

[0049] 其转录被组蛋白脱乙酰酶抑制剂改变的基因包括：

[0050] 1) 由 HDAC 抑制剂诱导的基因：细胞周期 (p1 和细胞周期蛋白 E)、促凋亡的 (Bak、BAX、CD95 及其配体凝溶胶蛋白、GADD45β、p53、Apaf-1 DFF45a、Bim、BAD、TRAIL、DR5、Fas 及其配体以及胱天蛋白酶 9、-8 和 -3)、氧化还原成分（硫氧还蛋白结合蛋白 -1、硫氧还蛋白、谷氧还蛋白和金属硫蛋白 IL)、染色质结构（组蛋白 H2B)、视黄酸途径 (RAPβ)。

[0051] 2) 被 HDAC 抑制剂抑制的基因：细胞周期（细胞周期蛋白 D1 和 A 以及胸苷酸合酶）、抗凋亡的 (Bcl-2、Bcl-XL、c-FLIP、存活蛋白、XIAP)、血管生成因子（血管内皮生长因子和 HIF-Loc)、脂多糖诱导的炎性细胞因子 (TNF-a、IFN-g 及 IL-1b 和 -6)、信号转导及转录激活蛋白 5-控制的基因 (STAT5)。

[0052] HDAC 酶或同种型似乎参与许多不同类型的癌症。HDAC 抑制剂对 HDAC 的抑制导致多重期望的抗癌效果，例如但不限于：(i) 癌细胞增殖的抑制；(ii) 癌细胞的凋亡（细胞死亡）的诱导；(iii) 细胞周期调控；(iv) 肿瘤抑制基因的诱导；以及 (v) 肿瘤血管生成的阻断（新肿瘤血管的发育）。由 HDAC 抑制剂提供的这些多重效果提供了治疗癌症的方法。

[0053] 对组蛋白脱乙酰酶(HDAC)作为药物开发目标的关注已经集中于HDAC在调节与细胞周期进程和癌症发展和进展相关的基因中所起的作用(Kramer等,Trends Endocrinol. Metab.12,294-300,(2001))。一些研究已经表明,用HDAC抑制剂对各种细胞系的处理导致组蛋白蛋白质的高度乙酰化和细胞周期停滞在G_1晚期或G_2/M过渡期。参与细胞周期并且已显示被HDAC抑制剂上调的基因包括p21、p27、p53和细胞周期蛋白E。已经报道,细胞周期蛋白A和细胞周期蛋白D被HDAC抑制剂下调。在肿瘤细胞系中,一些研究已经表明,用HDAC抑制剂处理导致生长抑制、生长停滞、终末分化和/或细胞凋亡。体内研究已证明了因用HDAC抑制剂处理而导致的肿瘤生长抑制和肿瘤转移的减少。

[0054] 异常HDAC活性与癌症的最明显的联系发生在急性早幼粒细胞白血病中。在这种情况下,染色体易位导致视黄酸受体RARα与早幼粒细胞白血病(PML)或早幼粒细胞白血病锌指(PLZF)蛋白质的融合。PML-RARα和PLZF-RARα两者均通过经由SMRT-mSin3-HDAC复合物的异常募集抑制视黄酸调节的基因而促进白血病的进展(Lin等,Nature 391,811-814(1998));Grignani等,Nature 391,815-818(1998))。PML-RARα形式的疾病能用视黄酸治疗,而PLZF-RARα形式对这种治疗具有抗性。对于患有抗视黄酸形式的疾病的患者,向给药方案中添加HDAC抑制剂丁酸钠导致临床的和细胞发生的完全缓解(Warrell等,J.Natl.Cancer.Inst.90,1621-1625,(1998))。HDAC还与亨廷顿病相关(Steffan等,Nature413:739-744,“Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in Drosophila”)。

[0055] 一般来说,几乎所有针对HDAC的抑制剂都是广谱化合物,以同等的效力抑制所有HDAC同种型。这些广谱HDAC抑制剂在体外在大量肿瘤细胞系中引起分化诱导、生长停滞和/或细胞凋亡。

[0056] 广谱HDAC抑制剂(泛HDAC抑制剂)的临床给药与许多剂量限制性毒性相关。其中包括血小板减少和其他血液毒性、QTc延长和其他心脏毒性、恶心、发烧、疲劳以及食欲不振(例如,参见Clinical Cancer Research 2003,9(10),3578-3588;Clinical Cancer Research2002,8(7),2142-2148;和Proceedingsof the American Association of Cancer Research 2005,46,Abs 3978)。与泛选择性抑制剂相反,只选择性地抑制一种HDAC同种型的选择性HDAC抑制剂有望用于生产具有改善的毒性谱的药物。

[0057] 在数项使用泛HDAC抑制剂的临床试验中已经报道了在人体中的不良反应。最初是针对肿瘤应用而设计,当考虑到其治疗效果和癌症的高死亡率时,此类毒性可能不是至关重要的。

[0058] 本文描述了HDAC8抑制剂化合物。相比其他HDAC同种型(例如HDAC 1、2、3、6、10和11),本文描述的化合物选择性地抑制HDAC8。

[0059] 如本文所述,HDAC8主要在胰腺中的胰岛的δ细胞中、在小肠上皮细胞中以及在神经内分泌细胞中表达。值得注意的是,δ细胞表达和分泌促生长素抑制素,即一种抑制胰岛素和生长激素的分泌的肽类激素。不被理论所束缚,据认为HDAC8活性推动促生长素抑制素在δ细胞中的表达。因此,抑制HDAC8活性预期会减少促生长素抑制素从δ细胞中的表达和分泌,继而提高全身性胰岛素和生长激素水平。

[0060] 本文描述了通过向受试者施用选择性HDAC8抑制剂组合物来抑制受试者的促生长素抑制素表达的方法。另外,本文描述了通过向受试者施用选择性HDAC8抑制剂来治疗

患有胰岛素缺乏或生长激素缺乏的受试者的方法。

T 细胞淋巴瘤或白血病

[0061] HDAC8 以异常高的水平在诸如 Jurkat、HuT78、K562、PC3 和 OVCR-3 等肿瘤细胞系中表达。事实上，如本文所述，抑制 HDAC8 活性通过细胞凋亡减少 T 细胞来源的肿瘤细胞（例如 Jurkat 细胞）的增殖。相反，HDAC8 抑制不影响非癌性细胞（例如外周血单核细胞）或除 T 细胞来源的细胞系外的肿瘤细胞系的增殖。因此，选择性 HDAC8 抑制剂可用于减缓或阻止 T 细胞来源的癌症的进展，而对非癌性细胞具有减少的毒性或无毒性。

[0062] 本文描述了通过向患有 T 细胞淋巴瘤的受试者施用选择性 HDAC8 抑制剂组合物来治疗该受试者的方法。本文还描述了通过向患有 T 细胞淋巴瘤的受试者施用已经在体外暴露于选择性 HDAC8 抑制剂组合物的自体 T 细胞群体来治疗该受试者的方法。

[0063] 在一些实施方案中，选择性 HDAC8 抑制剂化合物和其组合物用于治疗患有 T 细胞淋巴瘤，例如外周 T 细胞淋巴瘤、淋巴母细胞淋巴瘤、皮肤 T 细胞淋巴瘤或成人 T 细胞淋巴瘤的受试者。

[0064] 在一些实施方案中，T 细胞淋巴瘤的治疗方法包括向受试者施用治疗有效量的选择性 HDAC8 抑制剂药物组合物。

[0065] 在其他实施方案中，T 细胞淋巴瘤的治疗包括除选择性 HDAC8 抑制剂药物组合物外，还施用任意组合的本文所述的一种或多种另外的抗癌剂。

[0066] 本文所述的方法包括以治疗有效量施用含有足以在体内降低 HDAC8 脱乙酰酶活性的量的选择性 HDAC8 抑制剂的药物组合物。在一些实施方案中，源自于待治疗受试者的细胞（即自体细胞）在体外暴露于含有足以在体外降低 HDAC8 脱乙酰酶活性的量的选择性 HDAC8 抑制剂组合物的药物组合物。

[0067] 在一个实施方案中，来自患有 T 细胞淋巴瘤的供体受试者的 T 细胞在能有效地选择性杀死转化 T 细胞的浓度的选择性 HDAC8 抑制剂的存在下在体外进行培养和扩增。然后，将不含转化 T 细胞的扩增的 T 细胞群体引入至供体受试者。T 细胞培养、体外扩增和体内转移在例如 Porter 等，(2006)，Blood，107(4)：1325-1331；Rapoport 等，(2005)，Nat.Med.，1230-1237；Laport 等，(2003)，Blood，102(6)：2004-2013 中进行了描述。

细胞因子调节的健康状况

[0068] 在一些实施方案中，向受试者施用治疗有效量的选择性 HDAC8 抑制剂以减少一种或多种炎性细胞因子（例如 IL-1β）的分泌。

[0069] 在一些实施方案中，向受试者施用选择性 HDAC8 抑制剂化合物以降低一种或多种炎性细胞因子的全身性水平，该炎性细胞因子包括例如 IL-1β、IL-6、IL-18、TNF-α、MCP-1 或 MIP-1α。

[0070] 如本文所述，本文所述的选择性 HDAC8 抑制剂化合物减少包括但不限于白介素 -1β（IL-1β）的促炎细胞因子的分泌。因此，HDAC8 是参与细胞因子分泌的 HDAC 酶。选择性 HDAC8 抑制剂化合物的使用提供了减少细胞因子分泌而具有减弱的毒性的方法，这是由于其对一种 HDAC 同种型的选择性抑制（相比于抑制所有 HDAC 同种型的泛 -HDAC 抑制剂的使用）。

[0071] 本文所述的选择性 HDAC8 抑制剂化合物以剂量依赖性方式抑制脂多糖 (LPS) 和 / 或 ATP 刺激的 IL-1β 从纯化的人外周血单核细胞 (PBMC) 以及单核细胞系 THP-1 的分泌。

在一些实施方案中，抑制的 EC_{50} 在从约 0.5 微摩尔至约 5 微摩尔的范围内。

[0072] IL-1β 的产生和分泌是通过蛋白质分泌的非经典途径进行的，其涉及钾流出、胱天蛋白酶原的自催化加工、活性胱天蛋白酶 -1 对 IL-1β 前体的切割、钙离子流入以及包括 PLA-2 在内的特定磷脂酶的激活。在一些实施方案中，本文所述的选择性 HDAC8 抑制剂化合物抑制这种分泌途径中的一个或多个步骤。

[0073] 如本文所述，选择性 HDAC8 抑制剂用于治疗由 IL-1β 分泌和活性介导或与之相关的疾病或状况。在某些自身免疫性疾病或状况中，IL-1β 为疾病或状况的体征和症状作出贡献（例如 Burger 等，Best Practice&Research Clinical Rheumatology，Vol.20，No.5，PP.879-896，2006；Dayer 等，Current Opinions in Rheum.，2001，13：170-176；Abramson 等，Rheumatology，2002；41；972-980）；选择性 HDAC8 抑制剂化合物用于治疗此类疾病或状况。如本文所述，选择性 HDAC8 抑制剂化合物用于抑制 IL-1β 分泌，因此可用于治疗与 IL-1β 分泌和活性相关联的疾病或状况，包括但不限于：骨关节炎、类风湿性关节炎、脓毒性关节炎、痛风、假痛风、幼年型关节炎、斯蒂尔病、强直性脊柱炎、系统性红斑狼疮 (SLE)、Henoch- Schönlein 紫癜、牛皮癣关节炎、反应性关节炎（莱特尔综合征）、血色素沉着病、肝炎、韦格纳肉芽肿病、家族性地中海热 (FMF)、HIDS（高免疫球蛋白血症 D 和周期性发热综合征）、TRAPS(TNF-α 受体相关的周期性发热综合征）、炎性肠病、克罗恩病、溃疡性结肠炎、回归热、贫血、白细胞增多、哮喘、慢性阻塞性肺病、肌痛；成人斯蒂尔病、全身性发作幼年特发性关节炎、狼疮性关节炎、强直性脊柱炎、家族性地中海热 (FMF)、TNF 受体相关的周期性综合征 (TRAPS)、高免疫球蛋白血症 D 伴周期性发热综合征 (HIDS)、Blau 综合征、FCAS、MWS、新生儿发病多系统炎症性疾病 (NOMID) 和 Cryopyrin 相关的周期性综合征 (CAPS)、家族性冷自身炎症性综合征 (FCAS)；Muckle-Wells 综合征 (MWS)、新生儿发病多系统炎症性疾病 (NOMID)；慢性婴儿神经、皮肤、关节综合征 (CINCA)；cryopyrin 相关的周期性综合征 (CAPS)；化脓性不育性关节炎、坏疽性脓皮病和痤疮综合征 (PAPA)。

[0074] 在进一步的实施方案中，本文所述的方法用于治疗炎性疾病，其包括但不限于：哮喘、炎性肠病、阑尾炎、眼睑炎、细支气管炎、支气管炎、粘液囊炎、子宫颈炎、胆道炎、胆囊炎、结肠炎、结膜炎、膀胱炎、泪腺炎、皮炎、皮肌炎、脑炎、心内膜炎、子宫内膜炎、肠炎、小肠结肠炎、上髁炎、附睾炎、筋膜炎、纤维织炎、胃炎、胃肠炎、肝炎、化脓性汗腺炎、喉炎、乳腺炎、髓膜炎、脊髓炎心肌炎、肌炎、肾炎、卵巢炎、睾丸炎、骨炎、耳炎、胰腺炎、腮腺炎、心包炎、腹膜炎、咽炎、肋膜炎、静脉炎、局限性肺炎、肺炎、直肠炎、前列腺炎、肾盂肾炎、鼻炎、输卵管炎、窦炎、口腔炎、滑膜炎、肌腱炎、扁桃体炎、葡萄膜炎、阴道炎、脉管炎和外阴炎。

[0075] 在另外其他的实施方案中，本文所述的方法用于治疗炎性皮肤状况。炎性皮肤状况是其中在没有明显的或已知的感染性病因的情况下炎性细胞（例如多形核中性粒细胞和淋巴细胞）浸润皮肤的皮肤状况。炎性皮肤状况的症状通常包括红斑（泛红）、水肿（肿胀）、疼痛、瘙痒、表面温度升高和功能丧失。如本文所用，炎性皮肤状况包括但不限于：变应性接触性皮炎、荨麻疹皮炎、牛皮癣、湿疹和相关状况、昆虫叮咬、红皮病、蕈样真菌病和相关状况、坏疽性脓皮病、多形红斑、红斑痤疮、甲癣以及痤疮和相关状况，但不包括除牛皮癣及其相关状况。

[0076] 在一些实施方案中，本文所述的方法用于治疗自身免疫性疾病，包括但不限于类风湿性关节炎、牛皮癣关节炎、骨关节炎、斯蒂尔病、幼年型关节炎、狼疮、糖尿病、重

症肌无力、桥本氏甲状腺炎 (Hashimoto's thyroiditis)、Ord 甲状腺炎、格雷夫斯病 (Graves' disease)、合格伦综合征 (Sjögren's syndrome)、多发性硬化、格林 - 巴利综合征 (Guillain-Barré syndrome)、急性播散性脑脊髓炎、阿狄森病、斜视眼阵挛 - 肌阵挛综合征、强直性脊柱炎、抗磷脂抗体综合征、再生障碍性贫血、自身免疫性肝炎、腹腔病、肺出血肾炎综合征 (Goodpasture's syndrome)、特发性血小板减少性紫癜、视神经炎、硬皮病、原发性胆汁性肝硬化、莱特尔综合征 (Reiter's syndrome)、高安氏动脉炎 (Takayasu's arteritis)、颞动脉炎、温型自身免疫性溶血性贫血、韦格纳肉芽肿病、牛皮癣、普秃、贝赛特氏症 (Behçet's disease)、慢性疲劳、自主神经机能异常、子宫内膜异位症、间质性膀胱炎、神经性肌强直、硬皮病和外阴痛。

[0077] 在一些实施方案中，本文所述的方法用于治疗异种免疫状况或疾病，包括但不限于移植物抗宿主病、移植、输血、过敏性反应、变态反应 (例如，对植物花粉、乳胶、药物、食物、昆虫毒物、动物毛发、动物皮屑、尘螨或蟑螂腮片的变态反应)、I 型超敏反应、变应性结膜炎、变应性鼻炎和特应性皮炎。

[0078] 患者的慢性炎症已与癌症的发展相关联 (Coussens 等，Nature，420，860-867，2002)。与慢性炎症相关的癌症包括但不限于 :肺癌、食道癌、胃癌、胰腺癌、子宫颈癌、膀胱癌、前列腺癌和结肠直肠癌。炎性微环境作为致病因素在癌症病因学中的作用也得到了以下发现的支持 :非甾体抗炎药 (NSAID) 的定期使用与结肠直肠癌、乳腺癌和胃癌发生率的降低相关。促炎细胞因子是慢性炎症应答的介质并对恶化过程有效果。

[0079] 促炎细胞因子参与癌发生及恶性转化、肿瘤生长、侵袭和转移。促炎细胞因子在肿瘤内或其附近的持续表达发挥了多种效应，包括但不限于 :不断增长的恶性细胞的生长和侵袭、转移、肿瘤发生、免疫介导的机制的激活，从而导致肿瘤细胞的破坏和肿瘤生长的抑制。已经报道，IL-1β 转染的肿瘤细胞不能诱导有效的抗肿瘤免疫应答。在几种人类癌症中，恶性细胞或微环境的局部 IL-1β 表达已与侵袭性肿瘤生长和预后不良有关。

[0080] 在 IL-1β 转染的纤维肉瘤细胞中，观察到了参与侵袭的基因 MMP-2 和 MMP-9 和 TGFβ 的上调，这与在 IL-1α 转染的纤维肉瘤细胞中这些基因的关闭相反。IL-1β 被认为也通过开启血管发生和通过诱导炎性分子如 MMP、类肝素酶、趋化因子或恶性细胞或内皮细胞上的整联蛋白而增强已存在的肿瘤细胞的侵袭力，从而导致肿瘤的传播和转移。IL-1β 诱导分泌生长和侵袭促进因子，例如基质金属蛋白酶和血管生成因子 (即 VEGF 和 bFGF 和 ELR- 阳性 CXC 趋化因子，即 IL-8 和 MCP-1)。(Apte 等，Cancer Biology 中的论文集，vol. 12，2002，277-290)。

[0081] 分泌的 IL-1β 已经与肿瘤生长和侵袭相关联。在恶性细胞或肿瘤的微环境中，例如通过使用选择性 HDAC8 化合物对 IL-1β 分泌的抑制提供了一种癌症治疗方法。

[0082] 因此在一个实施方案中，本文所述的选择性 HDAC8 化合物用于癌症治疗。在一个实施方案中，本文所述的选择性 HDAC8 化合物用于肉瘤的治疗。在另一个实施方案中，本文所述的选择性 HDAC8 化合物用于肉瘤的治疗，该肉瘤选自 :软组织腺泡状肉瘤、血管肉瘤、皮肤纤维肉瘤、硬纤维瘤、结缔组织增生性小圆细胞肿瘤、骨外软骨肉瘤、骨外骨肉瘤、纤维肉瘤、血管外皮细胞瘤、血管内皮肉瘤、卡波西肉瘤 (kaposi's sarcoma)、平滑肌肉瘤、脂肪肉瘤、淋巴管肉瘤、恶性纤维组织细胞瘤、神经纤维肉瘤、横纹肌肉瘤、滑膜肉瘤、阿斯瘤

(askin's tumor)、尤文氏瘤 (ewing's)、恶性血管内皮细胞瘤、恶性神经鞘瘤、骨肉瘤、软骨肉瘤。

[0083] 上述各种状况的症状、诊断试验和预后试验是已知的。参见,例如,"Harrison's Principles of Internal Medicine©",第十六版,2004,The McGraw-Hill Companies, Inc.。

[0084] 在各种本文所述的实施方案中,受试者患有超过一种通过施用治疗有效量的选择性 HDAC8 抑制剂组合物进行治疗的状况。因此,应当理解,本文所述的方法有效地用于治疗患有适合于通过施用选择性 HDAC8 抑制剂组合物进行治疗的健康状况任意组合的受试者。例如,在一些实施方案中,患有 T 细胞淋巴瘤的受试者还患有炎性状况,反之亦然。

化合物

[0085] 本文所述的化合物、其药学上可接受的盐、药学上可接受的 N- 氧化物、药学活性代谢物、药学上可接受的前药或药学上可接受的溶剂化物抑制 HDAC8 活性,并用于治疗其中对 HDAC8 活性的抑制提供益处的患者。本文所述的化合物是 HDAC8 抑制剂化合物。

[0086] 在本文所述方法的一些实施方案中,选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 比对 HDAC1、HDAC2、HDAC3、HDAC6、HDAC10 或 HDAC11 的 IC_{50} 低至少约 10 倍。在本文所述任何方法的一些实施方案中,选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 小于约 100 nM,并且比对 HDAC1、HDAC2、HDAC3、HDAC6、HDAC10 或 HDAC11 的 IC_{50} 低至少约 10 倍。在本文所述任何方法的一些实施方案中,选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 小于约 50nM,并且比该选择性抑制剂对 HDAC1、HDAC2、HDAC3、HDAC6、HDAC10 或 HDAC11 的 IC_{50} 低至少约 10 倍。

[0087] 在一些实施方案中,本文所述的选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 比对 HDAC1、HDAC2、HDAC3、HDAC6 和 HDAC10 的 IC_{50} 低至少约 15 倍。在一些实施方案中,本文所述的选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 比对 HDAC1、HDAC2、HDAC3、HDAC6 和 HDAC10 的 IC_{50} 低至少约 20 倍。在一些实施方案中,本文所述的选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 比对 HDAC1、HDAC2、HDAC3、HDAC6 和 HDAC10 的 IC_{50} 低至少约 100 倍。另外,本文所述的选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 小于约 100 nM,而对 HDAC1、HDAC2、HDAC3、HDAC6 和 HDAC10 的 IC_{50} 大于约 100 nM。

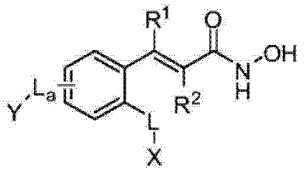
[0088] 在一些实施方案中,本文所述的选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 比对 HDAC1 的 IC_{50} 低至少约 10 倍。在一些实施方案中,本文所述的选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 比对 HDAC1 的 IC_{50} 低至少约 20 倍。在一些实施方案中,本文所述的选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 比对 HDAC1 的 IC_{50} 低至少约 40 倍。在一些实施方案中,本文所述的选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 比对 HDAC1 的 IC_{50} 低至少约 100 倍。在一些实施方案中,本文所述的选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 比对 HDAC1 的 IC_{50} 低至少约 150 倍。在又一些实施方案中,本文所述的选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 比对 HDAC1 的 IC_{50} 低至少约 200 倍。

[0089] 在一些实施方案中,本文所述的选择性 HDAC8 抑制剂对 HDAC8 的 IC_{50} 小于约 100 nM,并且比对其他 HDAC 同种型 (HDAC1、HDAC2、HDAC3、HDAC6、HDAC10) 的 IC_{50} 低至少约 20 倍,其中对其他 HDAC 同种型的 IC_{50} 大于约 100nM。

[0090] 在一些实施方案中,本文描述了选择性组蛋白脱乙酰酶 8(HDAC8) 抑制剂。在一些实施方案中,该选择性 HDAC8 抑制剂对组蛋白脱乙酰酶 8 活性的 IC_{50} 比该选择性 HDAC8 抑

制剂对组蛋白脱乙酰酶 1、组蛋白脱乙酰酶 2、组蛋白脱乙酰酶 3、组蛋白脱乙酰酶 6、组蛋白脱乙酰酶 10 或组蛋白脱乙酰酶 11 活性的 IC_{50} 低至少约 10 倍。

[0091] 在一个方面是具有式 (I) 结构的化合物：



式(I)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

L 和 L_a 各自独立地是键、O、S、NR^3、$-NR^{10}C(=O)-R^{11}$、$S(=O)$、$S(=O)_2$、$NHS(=O)_2$、$-C_1$-C_6 亚烷基 -、$-C_2$-C_6 亚烯基 -、$-C_2$-C_6 亚炔基 -、$-C_1$-C_6 亚杂烷基 -、$-C_1$-C_6 亚烷基 -O-、$-C_1$-C_3 亚烷基 -O-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3-$、$-C_1$-C_3 亚烷基 $-NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-C(=O)NR^3-$、$-C_1$-C_3 亚烷基 $-C(=O)NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3C(=O)-$、$-C_1$-C_3 亚烷基 $-NR^3C(=O)-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -S-、$-C_1$-C_3 亚烷基 -S-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-S(=O)-$、$-C_1$-C_3 亚烷基 $-S(=O)-C_1$-C_3 亚烷基、$-C_1$-C_6 亚烷基 $-S(=O)_2-$、$-C_1$-C_3 亚烷基 $-S(=O)_2-C_1$-C_3 亚烷基、$-C(=O)-$ 或 $-C(=O)-C_1$-C_6 亚烷基；

X 是选自芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 X 是取代的，那么 X 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

Y 是 H 或选自 C_1-C_6 烷基、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 Y 是取代的，那么 Y 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^3 是 H、C_1-C_6 烷基、苯基或苄基；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0092] 在一个实施方案中是取代的肉桂酸羟基酰胺化合物，其中在 2- 位上的取代基是 L-X，其中：

L 是键、O、S、NR^3、S(=O)、$S(=O)_2$、$-C_1$-C_6 亚烷基 -、$-C_2$-C_6 亚烯基 -、$-C_2$-C_6 亚炔基 -、$-C_1$-C_6 亚杂烷基 -、$-C_1$-C_6 亚烷基 -O-、$-C_1$-C_3 亚烷基 -O-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -NR^3-、$-C_1$-C_3 亚烷基 -NR^3-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -C(=O)NR^3-、$-C_1$-C_3 亚烷基 -C(=O)NR^3-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -NR^3C(=O)-、$-C_1$-C_3 亚烷基 -NR^3C(=O)-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -S-、$-C_1$-C_3 亚烷基 -S-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -S(=O)-、$-C_1$-C_3 亚烷基 -S(=O)-C_1-C_3 亚烷基、$-C_1$-C_6 亚烷基 -S(=O)$_2$-、$-C_1$-C_3 亚烷基 -S(=O)$_2$-C_1-C_3 亚烷基、-C(=O)- 或 -C(=O)-C_1-C_6 亚烷基；

X 是选自芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 X 是取代的，那么 X 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、-C(=O)R^{11}、-S-R^{11}、-S(=O)-R^{11}、-S(=O)$_2$-R^{11}、-NR^{10}C(=O)-R^{11}、-C(=O)N(R^{10})$_2$、-S(=O)$_2$N(R^{10})$_2$、-NR^{10}S(=O)$_2$-R^{11}、-OC(=O)N(R^{10})$_2$、-NR^{10}C(=O)O-R^{11}、-OC(=O)O-R^{11}、-NHC(=O)NH-R^{11}、-OC(=O)-R^{11}、-N(R^{10})$_2$、$-C_1$-C_2 烷基 N(R^{10})$_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

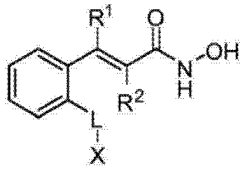
或其活性代谢物、药学上可接受的溶剂化物、药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0093] 对于任何和所有实施方案，取代基选自所列备选基团的子集。例如，在一些实施方案中，L 是 O、S 或 NR^3。在其他实施方案中，L 是 O。在一些实施方案中，L 是 S。在一些实施方案中，L 是 NR^3，其中 R^3 是氢。在一个实施方案中，L 是 NR^3，其中 R^3 是 C_1-C_6 烷基。在另一个实施方案中，L 是 NR^3，其中 R^3 是甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。在另一个实施方案中，L 是 NR^3，其中 R^3 是甲基。在又一个实施方案中，L 是键。在又一个实施方案中，L 是 S(=O) 或 $S(=O)_2$。在另一个实施方案中，L 是 $-C_1$-C_6 亚烷基 -、$-C_2$-C_6 亚烯基 - 或 $-C_2$-C_6 亚炔基 -。在又一个实施方案中，L 是 C_1-C_6 亚烷基，其选自亚甲基、亚乙基或亚丙基。在另一个实施方案中，L 是 $-C_1$-C_6 亚杂烷基 -、$-C_1$-C_6 亚烷基 -O-、$-C_1$-C_3 亚烷基 -O-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -NR^3-、$-C_1$-C_6 亚烷基 -S-、$-C_1$-C_3 亚烷基 -S-C_1-C_3 亚烷基 - 或 $-C_1$-C_3 亚烷基 -NR^3-C_1-C_3 亚烷基 -。在一个实施方案中，L 是 $-CH_2$-S-。在另一个实施方案中，L 是 $-CH_2NR^3$-。在另一个实施方案中，L 是 $-CH_2NR^3$，其中 R^3 是 H。在一个实施方案中，L 是 $-CH_2$-O-。在又一个实施方案中，L 是 $-C_1$-C_6 亚烷基 -C(=O)NR^3-、$-C_1$-C_3 亚烷基 -C(=O)NR^3-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -NR^3C(=O)- 或 $-C_1$-C_3 亚烷基 -NR^3C(=O)-C_1-C_3 亚烷基 -。在又一个实施方案中，L 是 $-C_1$-C_6 亚烷基 -S(=O)-、$-C_1$-C_3 亚烷基 -S(=O)-C_1-C_3 亚烷基、$-C_1$-C_6 亚烷基 -S(=O)$_2$-、$-C_1$-C_3 亚烷基 -S(=O)$_2$-C_1-C_3 亚烷基。在又一个实施

方案中，L 是 -C(= O)- 或 -C(= O)-C_1-C_6 亚烷基。

[0094] 本文还描述了式 (I) 的化合物，其中 R^1 和 R^2 各自独立地是 H 或 C_1-C_6 烷基。在另一个实施方案中，R^1 是 H。在又一个实施方案中，R^2 是 H。在另一个实施方案中，R^1 和 R^2 都是 H。在又一个实施方案中，R^1 是 C_1-C_6 烷基，其选自甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、正戊基或正己基。在另一个实施方案中，R^2 是 C_1-C_6 烷基，其选自甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、正戊基或正己基。

[0095] 在另一个实施方案中是式 (II) 的化合物：



式(II)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

L 是键、O、S、NR^3、-NR^{10}C(= O)-R^{11}、S(= O)、S(= O)$_2$、-C_1-C_6 亚烷基 -、-C_2-C_6 亚烯基 -、-C_2-C_6 亚炔基 -、-C_1-C_6 亚杂烷基 -、-C_1-C_6 亚烷基 -O-、-C_1-C_3 亚烷基 -O-C_1-C_3 亚烷基 -、-C_1-C_6 亚烷基 -NR^3-、-C_1-C_3 亚烷基 -NR^3-C_1-C_3 亚烷基 -、-C_1-C_6 亚烷基 -C(= O)NR^3-、-C_1-C_3 亚烷基 -C(= O)NR^3-C_1-C_3 亚烷基 -、-C_1-C_6 亚烷基 -NR^3C(= O)-、-C_1-C_3 亚烷基 -NR^3C(= O)-C_1-C_3 亚烷基 -、-C_1-C_6 亚烷基 -S-、-C_1-C_3 亚烷基 -S-C_1-C_3 亚烷基 -、-C_1-C_6 亚烷基 -S(= O)-、-C_1-C_3 亚烷基 -S(= O)-C_1-C_3 亚烷基、-C_1-C_6 亚烷基 -S(= O)$_2$-、-C_1-C_3 亚烷基 -S(= O)$_2$-C_1-C_3 亚烷基、-C(= O)- 或 -C(= O)-C_1-C_6 亚烷基；

X 是选自芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 X 是取代的，那么 X 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、-NO_2、-CO_2R^{10}、-C(= O)R^{11}、-S-R^{11}、-S(= O)-R^{11}、-S(= O)$_2$-R^{11}、-NR^{10}C(= O)-R^{11}、-C(= O)N(R^{10})$_2$、-S(= O)$_2$N(R^{10})$_2$、-NR^{10}S(= O)$_2$-R^{11}、-OC(= O)N(R^{10})$_2$、-NR^{10}C(= O)O-R^{11}、-OC(= O)O-R^{11}、-NHC(= O)NH-R^{11}、-OC(= O)-R^{11}、-N(R^{10})$_2$、-C_1-C_2 烷基 N(R^{10})$_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

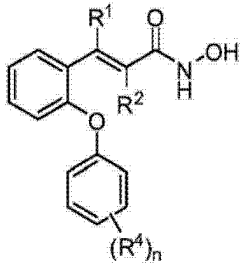
R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^3 是 H、C_1-C_6 烷基、苯基或苄基；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0096] 在另一个实施方案中是式 (IIA) 的化合物：



式(IIA)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

R^4 选自氢、卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、-NO_2、-CO_2R^{10}、-C(=O)R^{11}、-S-R^{11}、-S(=O)-R^{11}、-S(=O)$_2$-R^{11}、-NR^{10}C(=O)-R^{11}、-C(=O)N(R^{10})$_2$、-S(=O)$_2$N(R^{10})$_2$、-NR^{10}S(=O)$_2$-R^{11}、-OC(=O)N(R^{10})$_2$、-NR^{10}C(=O)O-R^{11}、-OC(=O)O-R^{11}、-NHC(=O)NH-R^{11}、-OC(=O)-R^{11}、-N(R^{10})$_2$、-C_1-C_2 烷基 N(R^{10})$_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

n 是 0 到 5 的整数；

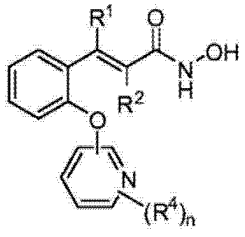
R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0097] 在一个实施方案中是式 (IIA) 的化合物，其中 R^1 和 R^2 各自独立地是 H。在另一个实施方案中是式 (IIA) 的化合物，其中 R^4 是卤素。在另一个实施方案中，R^4 是 Cl。在另一个实施方案中，R^4 是 F。在另一个实施方案中，R^4 是 Br。在另一个实施方案中，R^4 是 C_1-C_6 烷基。在又一个实施方案中，R^4 是甲基、乙基、正丙基、异丙基、异丁基和叔丁基。在另一个实施方案中，R^4 是甲基。在一个实施方案中，R^4 是 C_1-C_6 烷氧基。在另一个实施方案中，R^4 是甲氧基。在又一个实施方案中，R^4 是乙氧基。在另一个实施方案中是式 (IIA) 的化合物，其中 n 是 1。在另一个实施方案中，n 是 2。在又一个实施方案中，R^4 是在醚连接基团的对位取代的。在另一个实施方案中，R^4 是在醚连接基团的间位取代的。在又一个实施方案中，R^4 是在醚连接基团的邻位取代的。

[0098] 在另一个实施方案中是式 (IIB) 的化合物：



式(IIB)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

R^4 选自氢、卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

n 是从 0 至 4 的整数；

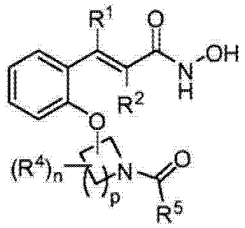
R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0099] 在一个实施方案中是式 (IIB) 的化合物，其中 R^1 和 R^2 各自独立地是 H。在一个实施方案中是式 (IIB) 的化合物，其中 R^4 是 H。在另一个实施方案中是式 (IIB) 的化合物，其中 R^4 是卤素。在另一个实施方案中，R^4 是 Cl。在又一个实施方案中，R^4 是 F。在另一个实施方案中，R^4 是 Br。在另一个实施方案中，R^4 是 C_1-C_6 烷基。在又一个实施方案中，R^4 是甲基、乙基、正丙基、异丙基、异丁基和叔丁基。在又一个实施方案中，R^4 是甲基。在一个实施方案中，R^4 是 C_1-C_6 烷氧基。在另一个实施方案中，R^4 是甲氧基。在又一个实施方案中，R^4 是乙氧基。在另一个实施方案中是式 (IIA) 的化合物，其中 n 是 1。在又一个实施方案中，n 是 2。在又一个实施方案中，R^4 是在醚连接基团的对位取代的。在另一个实施方案中，R^4 是在醚连接基团的间位取代的。在又一个实施方案中，R^4 是在醚连接基团的邻位取代的。

[0100] 在另一个实施方案中是式 (IIC) 的化合物：



式(IIC)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 $_1$-C_6 烷基；

R^4 和 R^5 各自独立地选自氢、卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、

取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

p 是从 0 到 4 的整数；

n 是从 0 到 5 的整数；

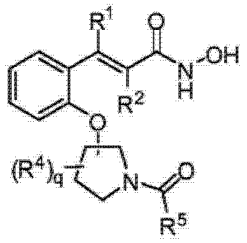
R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0101] 在一个实施方案中是式 (IIC) 的化合物，其中 R^1 和 R^2 各自独立地是 H。在另一个实施方案中是式 (IIC) 的化合物，其中 p 是 2。在另一个实施方案中是式 (IIC) 的化合物，其中 p 是 3。在又一实施方案中是式 (IIC) 的化合物，其中 p 是 4。

[0102] 在一个实施方案中是选自式 (IID) 的化合物：



式(IID)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

R^4 和 R^5 各自独立地选自氢、卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

q 是从 0 到 3 的整数；

R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

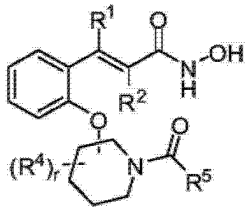
R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0103] 在一个实施方案中是式 (IID) 的化合物，其中 q 是 0。在另一个实施方案中是式 (IID) 的化合物，其中 R^1 和 R^2 各自独立地是 H。在又一个实施方案中是式 (IID) 的化合物，其中 R^5 是 C_1-C_6 烷基。在另一个实施方案中，R^5 是甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。在又一个实施方案中，R^5 是甲基。在又一个实施方案中，R^5 是异丙基。在又一个实施方案中，R^5 是芳基。在另一个实施方案中，R^5 是苯基。在又一个实施方案中，R^5 是杂

芳基。在一个实施方案中，R^5 选自吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、4- 氮杂吲哚基、5- 氮杂吲哚基、6- 氮杂吲哚基、7- 氮杂吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、咪唑并 [1,2-a] 吡啶基、噻吩并吡啶基和呋喃并吡啶基。在另一个实施方案中，R^5 是吡啶基。在又一个实施方案中，R^5 是呋喃基。在又一个实施方案中，R^5 是噻吩基。

[0104] 在另一个实施方案中是式 (IIE) 的化合物：



式(IIE)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

R^4 和 R^5 各自独立地选自氢、卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

r 是 0 到 4 的整数；

R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

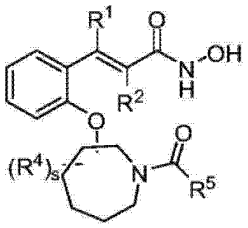
R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0105] 在一个实施方案中是式 (IIE) 的化合物，其中 r 是 0。在另一个实施方案中是式 (IIE) 的化合物，其中 R^1 和 R^2 各自独立地是 H。在又一个实施方案中是式 (IIE) 的化合物，其中 R^5 是 C_1-C_6 烷基。在另一个实施方案中，R^5 是甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。在又一个实施方案中，R^5 是甲基。在又一个实施方案中，R^5 是芳基。在另一个实施方案中，R^5 是苯基。在又一个实施方案中，R^5 是杂芳基。在一个实施方案中，R^5 选自吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、4- 氮杂吲哚基、5- 氮杂吲哚基、6- 氮杂吲哚基、7- 氮杂吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、咪唑并 [1,2-a] 吡啶基、噻吩并吡啶基

和呋喃并吡啶基。在另一个实施方案中，R^5 吡啶基。在又一个实施方案中，R^5 是呋喃基。在又一个实施方案中，R^5 是噻吩基。

[0106] 在又一个实施方案中是式（IIF）的化合物：



式(IIF)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

R^4 和 R^5 各自独立地选自氢、卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

s 是 0 到 5 的整数；

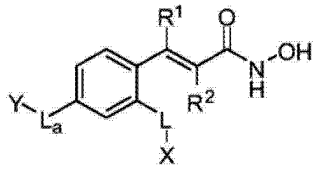
R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0107] 在一个实施方案中是式（IIF）的化合物，其中 s 是 0。在另一个实施方案中是式（IIF）的化合物，其中 R^1 和 R^2 各自独立地是 H。在又一个实施方案中是式（IIF）的化合物，其中 R^5 是 C_1-C_6 烷基。在另一个实施方案中，R^5 是甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。在又一个实施方案中，R^5 是甲基。在又一个实施方案中，R^5 是芳基。在另一个实施方案中，R^5 是苯基。在又一个实施方案中，R^5 是杂芳基。在一个实施方案中，R^5 选自吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、4- 氮杂吲哚基、5- 氮杂吲哚基、6- 氮杂吲哚基、7- 氮杂吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、咪唑并 [1,2-a] 吡啶基、噻吩并吡啶基和呋喃并吡啶基。在另一个实施方案中，R^5 是吡啶基。在又一个实施方案中，R^5 是呋喃基。在又一个实施方案中，R^5 是噻吩基。

[0108] 在又一实施方案中是式（III）的化合物：



式(III)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

L 和 L_a 各自独立地是键、O、S、NR^3、$-NR^{10}C(=O)-R^{11}$、$S(=O)$、$S(=O)_2$、$NHS(=O)_2$、$-C_1$-C_6 亚烷基 -、$-C_2$-C_6 亚烯基 -、$-C_2$-C_6 亚炔基 -、$-C_1$-C_6 亚杂烷基 -、$-C_1$-C_6 亚烷基 -O-、$-C_1$-C_3 亚烷基 -O-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3-$、$-C_1$-C_3 亚烷基 $-NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-C(=O)NR^3-$、$-C_1$-C_3 亚烷基 $-C(=O)NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3C(=O)-$、$-C_1$-C_3 亚烷基 $-NR^3C(=O)-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -S-、$-C_1$-C_3 亚烷基 -S-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-S(=O)-$、$-C_1$-C_3 亚烷基 $-S(=O)-C_1$-C_3 亚烷基、$-C_1$-C_6 亚烷基 $-S(=O)_2-$、$-C_1$-C_3 亚烷基 $-S(=O)_2-C_1$-C_3 亚烷基、$-C(=O)-$ 或 $-C(=O)-C_1$-C_6 亚烷基；

X 是选自芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 X 是取代的，那么 X 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

Y 是 H 或选自 C_1-C_6 烷基、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 Y 是取代的，那么 Y 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代和未取代的杂芳基；

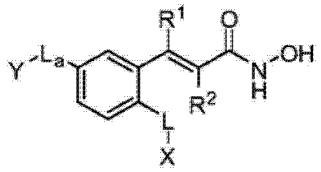
R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^3 是 H、C_1-C_6 烷基、苯基或苄基；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0109] 在又一实施方案中是式 (IV) 的化合物：



式(IV)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

L 和 L_a 各自独立地是键、O、S、NR^3、$-NR^{10}C(=O)-R^{11}$、$S(=O)$、$S(=O)_2$、$NHS(=O)_2$、$-C_1$-C_6 亚烷基 -、$-C_2$-C_6 亚烯基 -、$-C_2$-C_6 亚炔基 -、$-C_1$-C_6 亚杂烷基 -、$-C_1$-C_6 亚烷基 -O-、$-C_1$-C_3 亚烷基 -O-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3-$、$-C_1$-C_3 亚烷基 $-NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-C(=O)NR^3-$、$-C_1$-C_3 亚烷基 $-C(=O)NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3C(=O)-$、$-C_1$-C_3 亚烷基 $-NR^3C(=O)-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -S-、$-C_1$-C_3 亚烷基 -S-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-S(=O)-$、$-C_1$-C_3 亚烷基 $-S(=O)-C_1$-C_3 亚烷基、$-C_1$-C_6 亚烷基 $-S(=O)_2-$、$-C_1$-C_3 亚烷基 $-S(=O)_2-C_1$-C_3 亚烷基、$-C(=O)-$ 或 $-C(=O)-C_1$-C_6 亚烷基；

X 是选自芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 X 是取代的，那么 X 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

Y 是 H 或选自 C_1-C_6 烷基、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$S(=O)_2-R^{11}$、芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 Y 是取代的，那么 Y 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取

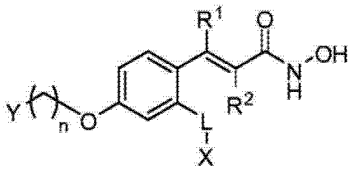
代或未取代的基团；

R^3 是 H、C_1-C_6 烷基、苯基或苄基；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0110] 在另一个实施方案中是式 (III) 的化合物，其中 L_a 是键。在一个实施方案中，L_a 是 O。在另一个实施方案中，L_a 是 NH。

[0111] 在另一个实施方案中是具有以下结构的式 (IIIa) 的化合物：



式(IIIa)

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

L 是键、O、S、NR^3、$-NR^{10}C(=O)-R^{11}$、$S(=O)$、$S(=O)_2$、$-C_1$-C_6 亚烷基 -、$-C_2$-C_6 亚烯基 -、$-C_2$-C_6 亚炔基 -、$-C_1$-C_6 亚杂烷基 -、$-C_1$-C_6 亚烷基 -O-、$-C_1$-C_3 亚烷基 -O-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3$-、$-C_1$-C_3 亚烷基 $-NR^3$-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-C(=O)NR^3$-、$-C_1$-C_3 亚烷基 $-C(=O)NR^3$-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3C(=O)$-、$-C_1$-C_3 亚烷基 $-NR^3C(=O)$-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -S-、$-C_1$-C_3 亚烷基 -S-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-S(=O)$-、$-C_1$-C_3 亚烷基 $-S(=O)$-C_1-C_3 亚烷基、$-C_1$-C_6 亚烷基 $-S(=O)_2$-、$-C_1$-C_3 亚烷基 $-S(=O)_2$-C_1-C_3 亚烷基、$-C(=O)$- 或 $-C(=O)$-C_1-C_6 亚烷基；

X 是选自芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 X 是取代的，那么 X 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

Y 是 H 或选自 C_1-C_6 烷基、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；如果 Y 是取代的，那么 Y 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

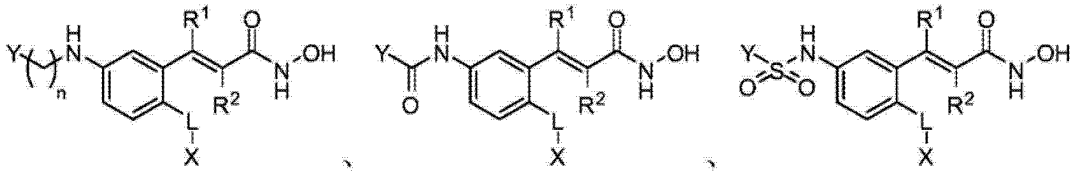
R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基或杂芳基的取代或未取代的基团；

n 是从 0 到 4 的整数；

R^3 是 H、C_1-C_6 烷基、苯基或苄基；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0112] 在另一个实施方案中是具有以下结构的化合物：



式(IVa)； 式(IVb)； 式(IVc)；

其中：

R^1 和 R^2 各自独立地是 H、OH、卤素或 C_1-C_6 烷基；

L 是键、O、S、NR^3、$-NR^{10}C(=O)-R^{11}$、$S(=O)$、$S(=O)_2$、$-C_1$-C_6 亚烷基 -、$-C_2$-C_6 亚烯基 -、$-C_2$-C_6 亚炔基 -、$-C_1$-C_6 亚杂烷基 -、$-C_1$-C_6 亚烷基 -O-、$-C_1$-C_3 亚烷基 -O-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3-$、$-C_1$-C_3 亚烷基 $-NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-C(=O)NR^3-$、$-C_1$-C_3 亚烷基 $-C(=O)NR^3-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-NR^3C(=O)-$、$-C_1$-C_3 亚烷基 $-NR^3C(=O)-C_1$-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 -S-、$-C_1$-C_3 亚烷基 -S-C_1-C_3 亚烷基 -、$-C_1$-C_6 亚烷基 $-S(=O)-$、$-C_1$-C_3 亚烷基 $-S(=O)-C_1$-C_3 亚烷基、$-C_1$-C_6 亚烷基 $-S(=O)_2-$、$-C_1$-C_3 亚烷基 $-S(=O)_2-C_1$-C_3 亚烷基、$-C(=O)-$ 或 $-C(=O)-C_1$-C_6 亚烷基；

X 是选自芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 X 是取代的，那么 X 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2 烷基 $N(R^{10})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

Y 是 H 或选自 C_1-C_6 烷基、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 Y 是取代的，那么 Y 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=$

O)NH-R^{11}、-OC(=O)-R^{11}、-N(R^{10})$_2$、-C_1-C_2 烷基 N(R^{10})$_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基；

R^{10} 是氢或选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_1-C_6 杂烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团；

n 是从 0 到 4 的整数；

R^3 是 H、C_1-C_6 烷基、苯基或苄基；

或其药学上可接受的盐、药学上可接受的 N- 氧化物或药学上可接受的前药。

[0113] 在一个实施方案中是式 (I)、(II)、(III)、(IIIa)、(IV)、(IVa)、(IVb) 或 (IVc) 的化合物，其中 X 是选自芳基、杂芳基、C_3-C_{10} 环烷基和 C_2-C_{10} 杂环烷基的取代或未取代的基团；其中如果 X 是取代的，那么 X 是被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代的：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、-NO_2、-CO_2R^{10}、-C(=O)R^{11}、-S-R^{11}、-S(=O)-R^{11}、-S(=O)$_2$-R^{11}、-NR^{10}C(=O)-R^{11}、-C(=O)N(R^{10})$_2$、-S(=O)$_2$N(R^{10})$_2$、-NR^{10}S(=O)$_2$-R^{11}、-OC(=O)N(R^{10})$_2$、-NR^{10}C(=O)O-R^{11}、-OC(=O)O-R^{11}、-NHC(=O)NH-R^{11}、-OC(=O)-R^{11}、-N(R^{10})$_2$、-C_1-C_2 烷基 N(R^{10})$_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基。

[0114] 在一些实施方案中是式 (I)、(II)、(III)、(IIIa)、(IV)、(IVa)、(IVb) 或 (IVc) 的化合物，其中 X 是取代或未取代的芳基基团。在另一个实施方案中，X 是取代或未取代的苯基基团。在又一个实施方案中，X 是取代或未取代的萘基。在又一个实施方案中，X 是未取代的苯基。

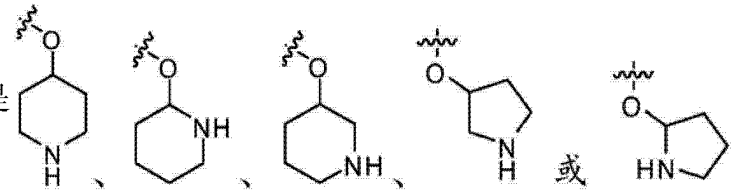
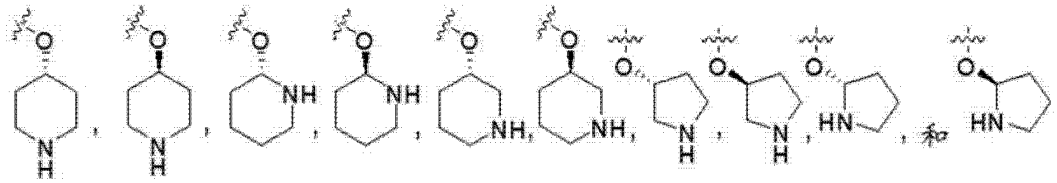
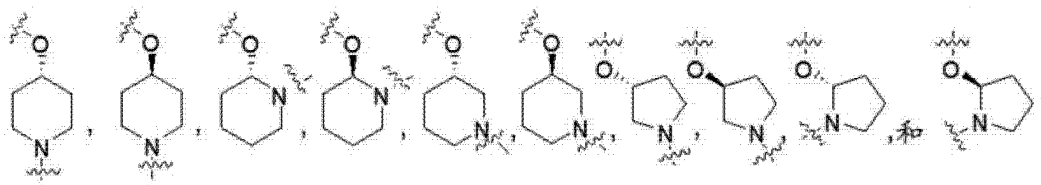
[0115] 在一些实施方案中，X 选自苯基、2- 甲基苯基、3- 甲基苯基、4- 甲基苯基、3,4- 二甲基苯基、2- 氟苯基、3- 氟苯基、4- 氟苯基、3,4- 二氟苯基、2- 氯苯基、3- 氯苯基、4- 氯苯基、2,4- 二氯苯基、3,4- 二氯苯基、3- 甲氧基苯基、4- 甲氧基苯基、3,5- 二甲氧基苯基、3,4,5- 三甲氧基苯基、2-(三氟甲基)- 苯基、3-(三氟甲基)- 苯基、4-(三氟甲基)- 苯基、2-(三氟甲氧基)- 苯基、3-(三氟甲氧基)- 苯基、4-(三氟甲氧基)- 苯基、2- 氯 -4- 氟苯基、3- 氯 -4- 氟苯基、2- 氟 -4- 氯苯基、3- 氟 -4- 氯苯基、2- 氯 -4- 甲氧基苯基、2,3- 二氯苯基、3- 甲氧基 -4- 氟苯基、3- 甲氧基 -5- 氟苯基、3- 甲氧基 -4- 氯苯基、3-(甲基磺酰基) 苯基、4-(甲基磺酰基) 苯基、2- 噻吩基、3- 噻吩基、2,3- 二氟苯基、2,4- 二氟苯基、3- 氟 -4- 甲氧基 - 苯基、2-(二氟甲氧基)- 苯基、3-(二氟甲氧基)- 苯基、4-(二氟甲氧基)- 苯基、N- 甲基磺酰基 -2- 氨基苯基、N- 甲基磺酰基 -3- 氨基苯基、N- 甲基磺酰基 -4- 氨基苯基、N- 苯基磺酰基 -2- 氨基苯基、N- 苯基磺酰基 -3- 氨基苯基、N- 苯基磺酰基 -4- 氨基苯基、2- 氨基苯基、3- 氨基苯基、4- 氨基苯基、2- 氨基苯基、3- 氨基苯基、4- 氨基苯基、2- 二甲基氨基苯基、3- 二甲基氨基苯基、4- 二甲基氨基苯基、N- 乙酰基 -2- 氨基苯基、N- 乙酰基 -3- 氨基苯基、N- 乙酰基 -4- 氨基苯基、N- 苯甲酰基 -2- 氨基苯基、N- 苯甲酰基 -3- 氨基苯基和 N- 苯甲酰基 -4- 氨基苯基。

[0116] 在其他实施方案中，X选自苯基、3-甲氧基苯基、4-甲氧基苯基、2-甲基苯基、3-甲基苯基、4-甲基苯基、2-氟苯基、3-氟苯基、4-氟苯基、2-氯苯基、3-氯苯基、4-氯苯基、3-氟-4-甲氧基苯基、4-(三氟甲氧基)-苯基、3,4-二氯苯基、2,4-二氯苯基、2-氯-4-氟苯基、3-氯-4-氟苯基、2-氟-4-氯苯基、3-氟-4-氯苯基、2-氯-4-甲氧基苯基、2,3-二氯苯基、3-甲氧基-4-氟苯基、3-甲氧基-5-氟苯基、3-甲氧基-4-氯苯基、3-(甲基磺酰基)苯基、4-(甲基磺酰基)苯基、2-噻吩基、3-噻吩基、2,3-二氟苯基、2,4-二氟苯基和3,4-二氟苯基。

[0117] 在另一个实施方案中是式(I)、(II)、(III)、(IIIa)、(IV)、(IVa)、(IVb)或(IVc)的化合物，其中X是取代的或未取代的杂芳基。在一个实施方案中，X是杂芳基，其选自吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、4-氮杂吲哚基、5-氮杂吲哚基、6-氮杂吲哚基、7-氮杂吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、咪唑并[1,2-a]吡啶基、噻吩并吡啶基和呋喃并吡啶基。在一个实施方案中，X是取代或未取代的2-吡啶基、3-吡啶基或4-吡啶基。在另一个实施方案中，2-吡啶基、3-吡啶基、4-吡啶基各自独立地被选自以下的1个、2个、3个、4个或5个基团所取代：卤素、C_1-C_6烷氧基、C_1-C_6氟烷氧基、氨基C_1-C_6烷氧基、C_1-C_3烷基氨基C_1-C_3烷氧基、羟基C_1-C_3烷基氨基C_1-C_3烷氧基、C_2-C_8杂环烷基C_1-C_3烷氧基、C_2-C_8杂环烷基C_1-C_2烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=O)-R^{11}$、$-N(R^{10})_2$、$-C_1$-C_2烷基$N(R^{10})_2$、C_1-C_6烷基、C_1-C_6氟烷基、C_2-C_6烯基、C_2-C_6炔基、C_1-C_6杂烷基、C_3-C_8环烷基、取代或未取代的C_2-C_{10}杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基。在又一个实施方案中，2-吡啶基、3-吡啶基、4-吡啶基各自独立地被选自卤素、C_1-C_6烷氧基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$和$-S-R^{11}$的1个、2个、3个、4个或5个基团所取代。在一个实施方案中，卤素是Cl。在另一个实施方案中，卤素是Br。在又一个实施方案，卤素是F。在又一个实施方案中，2-吡啶基、3-吡啶基、4-吡啶基各自独立地被CN所取代。在又一个实施方案中，2-吡啶基、3-吡啶基、4-吡啶基各自独立地被OH所取代。在又一个实施方案中，2-吡啶基、3-吡啶基、4-吡啶基各自独立地被至少两个取代基所取代。在又一个实施方案中，2-吡啶基、3-吡啶基、4-吡啶基各自独立地被至少三个取代基所取代。

[0118] 本文还描述了式(I)、(II)、(III)、(IIIa)、(IV)、(IVa)、(IVb)或(IVc)的化合物，其中X是取代或未取代的C_3-C_8环烷基。在一个实施方案中，C_3-C_8环烷基选自环戊基、环己基和环庚基。在一个实施方案中，环戊基、环己基和环庚基各自独立地被选自以下的1个、2个、3个、4个或5个基团所取代：卤素、C_1-C_6烷氧基、C_1-C_6氟烷氧基、氨基C_1-C_6烷氧基、C_1-C_3烷基氨基C_1-C_3烷氧基、羟基C_1-C_3烷基氨基C_1-C_3烷氧基、C_2-C_8杂环烷基C_1-C_3烷氧基、C_2-C_8杂环烷基C_1-C_2烷基、-CN、$-NO_2$、$-CO_2R^{10}$、$-C(=O)R^{11}$、$-S-R^{11}$、$-S(=O)-R^{11}$、$-S(=O)_2-R^{11}$、$-NR^{10}C(=O)-R^{11}$、$-C(=O)N(R^{10})_2$、$-S(=O)_2N(R^{10})_2$、$-NR^{10}S(=O)_2-R^{11}$、$-OC(=O)N(R^{10})_2$、$-NR^{10}C(=O)O-R^{11}$、$-OC(=O)O-R^{11}$、$-NHC(=O)NH-R^{11}$、$-OC(=$

O)-R^{11}、-N(R^{10})$_2$、-C_1-C_2 烷基 N(R^{10})$_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基。在又一个实施方案中，环戊基、环己基和环庚基各自独立地被选自卤素、C_1-C_6 烷氧基、-CN、-NO_2、-CO_2R^{10}、-C(=O)R^{11} 和 -S-R^{11} 的 1 个、2 个、3 个、4 个或 5 个基团所取代。在一个实施方案中，卤素是 Cl。在另一个实施方案中，卤素是 Br。在又一个实施方案中，卤素是 F。在又一个实施方案中，环戊基、环己基和环庚基各自独立地被 CN 所取代。在又一个实施方案中，环戊基、环己基和环庚基各自独立地被 OH 所取代。在又一个实施方案中，环戊基、环己基和环庚基各自独立地被至少两个取代基所取代。在又一个实施方案中，环戊基、环己基和环庚基各自独立地被至少三个取代基所取代。

[0119] 本文还描述了式 (I)、(II)、(III)、(IIIa)、(IV)、(IVa)、(IVb) 或 (IVc) 的化合物，其中 X 是取代或未取代的 C_2-C_{10} 杂环烷基，其选自喹噁基、二氧杂环己烯基、哌啶基、吗啉基、硫代吗啉基、噻噁基、四氢吡啶基、哌噁基、噁噁烷酮基、二氢吡咯基、二氢咪唑基、四氢呋喃基、四氢吡喃基、二氢噁唑基、环氧乙烷基、吡咯烷基、吡唑烷基、二氢噻吩基、咪唑烷酮基、吡咯烷酮基、二氢呋喃酮基、二氧杂环戊烷酮基、噻唑烷基、哌啶酮基、二氢吲哚基、四氢喹啉基、四氢异喹啉基和四氢噻吩基。在一个实施方案中，X 是取代或未取代的哌啶基或吡咯烷。在一个实施方案中是式 (I)、(II)、(III)、(IIIa)、(IV)、(IVa)、(IVb) 或 (IVc) 的化合物，其中 L-X 是 O-哌啶基或 O-吡咯烷，其中哌啶基或吡咯烷任选地被选自以下的 1 个、2 个、3 个、4 个或 5 个基团所取代：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、-CN、-NO_2、-CO_2R^{10}、-C(=O)R^{11}、-S-R^{11}、-S(=O)-R^{11}、-S(=O)$_2$-R^{11}、-NR^{10}C(=O)-R^{11}、-C(=O)N(R^{10})$_2$、-S(=O)$_2$N(R^{10})$_2$、-NR^{10}S(=O)$_2$-R^{11}、-OC(=O)N(R^{10})$_2$、-NR^{10}C(=O)O-R^{11}、-OC(=O)O-R^{11}、-NHC(=O)NH-R^{11}、-OC(=O)-R^{11}、-N(R^{10})$_2$、-C_1-C_2 烷基 N(R^{10})$_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基。在一个实施方案中，L-X 是  在另一个实施方案中，L-X 选自  ，其中 X 是未取代的哌啶或吡咯烷。在另一个实施方案中，L-X 是  其中 X 是取

代的哌啶或吡咯烷部分，其中取代基是在氮原子上。

[0120] 在另一个实施方案中，哌啶或吡咯烷是在氮原子上被 $-C(=O)R^{11}$ 所取代的，其中 R^{11} 是选自 C_1-C_6 烷基、C_1-C_6 氟烷基、C_3-C_8 环烷基、C_2-C_8 杂环烷基、芳基和杂芳基的取代或未取代的基团。在另一个实施方案中，哌啶或吡咯烷是在氮原子上被 $-C(=O)R^{11}$ 所取代的，其中 R^{11} 是取代或未取代的 C_1-C_6 烷基。在一个实施方案中，R^{11} 是甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。在另一个实施方案中，R^{11} 是甲基。在又一个实施方案中，R^{11} 是异丙基。

[0121] 在另一个实施方案中，哌啶或吡咯烷是在氮原子上被 $-C(=O)R^{11}$ 所取代的，其中 R^{11} 是取代或未取代的芳基。在一个实施方案中，该取代或未取代的芳基是苯基。在另一个实施方案中，该取代或未取代的芳基是萘基。在又一实施方案中，哌啶或吡咯烷是在氮原子上被 $-C(=O)R^{11}$ 所取代的，其中 R^{11} 是被至少一个选自以下的基团所取代的苯基：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、$-CN$、$-NO_2$、$-CO_2R^{12}$、$-C(=O)R^{13}$、$-S-R^{13}$、$-S(=O)-R^{13}$、$-S(=O)_2-R^{13}$、$-NR^{12}C(=O)-R^{13}$、$-C(=O)N(R^{12})_2$、$-S(=O)_2N(R^{12})_2$、$-NR^{12}S(=O)_2-R^{13}$、$-OC(=O)N(R^{12})_2$、$-NR^{12}C(=O)O-R^{13}$、$-OC(=O)O-R^{13}$、$-NHC(=O)NH-R^{13}$、$-OC(=O)-R^{13}$、$-N(R^{12})_2$、$-C_1$-C_2 烷基 $N(R^{12})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基，其中 R^{12} 是氢、C_1-C_6 烷基、苯基或苄基，且 R^{13} 是 C_1-C_6 烷基、苯基或苄基。在另一个实施方案中，R^{11} 是被卤素取代的苯基。在另一个实施方案中，R^{11} 是被选自 $-CN$、$-NO_2$ 或 SH 的取代基所取代的苯基。

[0122] 在另一个实施方案中，哌啶或吡咯烷是在氮原子上被 $-C(=O)R^{11}$ 所取代的，其中 R^{11} 是取代或未取代的杂芳基。在一个实施方案中，该取代或未取代的杂芳基是吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、4- 氮杂吲哚基、5- 氮杂吲哚基、6- 氮杂吲哚基、7- 氮杂吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、咪唑并 [1,2-a] 吡啶基、噻吩并吡啶基和呋喃并吡啶基。在另一个实施方案中，该取代或未取代的基团是吡啶基。在又一个实施方案中，哌啶或吡咯烷是在氮原子上被 $-C(=O)R^{11}$ 所取代的，其中 R^{11} 是被至少一个选自以下的基团所取代的吡啶：卤素、C_1-C_6 烷氧基、C_1-C_6 氟烷氧基、氨基 C_1-C_6 烷氧基、C_1-C_3 烷基氨基 C_1-C_3 烷氧基、羟基 C_1-C_3 烷基氨基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_3 烷氧基、C_2-C_8 杂环烷基 C_1-C_2 烷基、$-CN$、$-NO_2$、$-CO_2R^{12}$、$-C(=O)R^{13}$、$-S-R^{13}$、$-S(=O)-R^{13}$、$-S(=O)_2-R^{13}$、$-NR^{12}C(=O)-R^{13}$、$-C(=O)N(R^{12})_2$、$-S(=O)_2N(R^{12})_2$、$-NR^{12}S(=O)_2-R^{13}$、$-OC(=O)N(R^{12})_2$、$-NR^{12}C(=O)O-R^{13}$、$-OC(=O)O-R^{13}$、$-NHC(=O)NH-R^{13}$、$-OC(=O)-R^{13}$、$-N(R^{12})_2$、$-C_1$-C_2 烷基 $N(R^{12})_2$、C_1-C_6 烷基、C_1-C_6 氟烷基、C_2-C_6 烯基、C_2-C_6 炔基、C_1-C_6 杂烷基、C_3-C_8 环烷基、取代或未取代的 C_2-C_{10} 杂环烷基、取代或未取代的芳基和取代或未取代的杂芳基，其中 R^{12} 是氢、C_1-C_6 烷基、苯基或苄基，且 R^{13} 是 C_1-C_6 烷基、苯基或苄基。在另一个实施方案中，R^{11} 是 2- 吡啶、3- 吡啶或 4- 吡啶。在又一个实施方案中，杂芳基被卤素取代。在另一个实施方案中，R^{11} 是被选自 $-CN$、$-NO_2$ 或 SH 的取代基所取代的 2- 吡啶、3- 吡啶或 4- 吡啶。在又一个实施方案中，杂

芳基选自呋喃、噻吩、苯并噻吩、苯并噁唑、噁二唑或噁唑。在又一个实施方案中，杂芳基是任选地被卤素、C_1-C_6 烷基或 OH 取代的呋喃。

[0123] 在又一个实施方案中是式 (I)、(III)、(IIIa)、(IV)、(IVa)、(IVb) 或 (IVc) 的化合物，其中 Y 是取代或未取代的芳基。在一个实施方案中，Y 是取代的苯基。在另一个实施方案中，Y 是苯基。在一个实施方案中，该苯基被至少一个卤素取代。在另一个实施方案中，该苯基被至少两个卤素基团取代。在又一个实施方案中，该苯基被 F 基团取代。在另一个实施方案中，该苯基被至少一个 Cl 取代。在另一个实施方案中，被两个 Cl 基团取代。

[0124] 在又一个实施方案中是式 (I)、(III)、(IIIa)、(IV)、(IVa)、(IVb) 或 (IVc) 的化合物，其中 Y 是取代或未取代的杂芳基。在一个实施方案中，该取代或未取代的杂芳基选自吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、4- 氮杂吲哚基、5- 氮杂吲哚基、6- 氮杂吲哚基、7- 氮杂吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噁唑基、喹唑啉基、喹喔啉基、咪唑并 [1,2-a] 吡啶基、噻吩并吡啶基和呋喃并吡啶基。

[0125] 在一个实施方案中是式 (I)、(III)、(IIIa)、(IV)、(IVa)、(IVb) 或 (IVc) 的化合物，其中 Y 是吡啶。在另一个实施方案中，Y 是嘧啶。在又一个实施方案中，Y 是呋喃。在另一个实施方案中，Y 是噻吩。在又一个实施方案中，Y 是吲哚。

[0126] 在另一个实施方案中是式 (I)、(III)、(IIIa)、(IV)、(IVa)、(IVb) 或 (IVc) 的化合物，其中 Y 是取代或未取代的 C_2-C_{10} 杂环烷基。在另一个实施方案中，该 C_2-C_{10} 杂环烷基选自喹嗪基、二氧杂环己烯基、哌啶基、吗啉基、硫代吗啉基、噻嗪基、四氢吡啶基、哌嗪基、噁嗪烷酮基、二氢吡咯基、二氢咪唑基、四氢呋喃基、四氢吡喃基、二氢噁唑基、环氧乙烷基、吡咯烷基、吡唑烷基、二氢噻吩基、咪唑烷酮基、吡咯烷酮基、二氢呋喃酮基、二氧杂环戊烷酮基、噻唑烷基、哌啶酮基、二氢吲哚基、四氢喹啉基、四氢异喹啉基和四氢噻吩基。

[0127] 在另一个实施方案中是式 (I)、(III)、(IIIa)、(IV)、(IVa)、(IVb) 或 (IVc) 的化合物，其中 Y 是取代或未取代的哌嗪。在另一个实施方案中，哌嗪被 C_1-C_6 烷基取代。在另一个实施方案中，C_1-C_6 烷基选自甲基、乙基、正丙基、异丙基、正丁基、异丁基或叔丁基。在另一个实施方案中，哌嗪被甲基取代。

[0128] 本文设想到以上针对各种变量所述的基团的任意组合。应当理解，选择本文提供的化合物上的取代基和取代模式，以提供通过本文所述的技术合成的化学上稳定的化合物。

[0129] 在整个说明书中，选择其基团和取代基以提供稳定的部分和化合物。

化合物的其他形式

[0130] 在一些实施方案中，本文所述的化合物具有一个或多个立构中心，并且各个中心可以以 R 或 S 构型存在。本文提出的化合物包括所有非对映异构、对映异构和差向异构形式，及其适当的混合物。在一些实施方案中，立体异构体的分离通过色谱法完成。在其他实施方案中，通过将化合物的外消旋混合物与旋光性拆分剂反应以形成一对非对映异构化合物，分离非对映异构体，并回收光学纯的对映异构体，从而获得单个立体异构体。在一个实施方案中，使用本文所述的化合物的共价非对映衍生物进行对映异构体的拆分，也可使用

可解离的复合物（例如，结晶非对映异构盐）。非对映异构体具有不同的物理性质（例如，熔点、沸点、溶解度、反应性等），并且通过利用这些差异很容易地分离。在一些实施方案中，通过手性色谱法或通过基于溶解度差异的分离 / 拆分技术分离非对映异构体。随后通过任何不会导致外消旋化的实用手段将光学纯的对映异构体随拆分剂一起回收。适用于从化合物的外消旋混合物中拆分其立体异构体的技术的更详细说明可见于 Jean Jacques，Andre Collet，Samuel H.Wilen，“Enantiomers，Racemates and Resolutions”，John Wiley And Sons，Inc.，1981，均通过引用此类公开内容而并入本文。在又一个实施方案中，通过立体选择性合成获得立体异构体。

[0131] 在一些情况下，化合物作为互变异构体存在。所有的互变异构体都包括在本文所述的通式内。

[0132] 本文所述的方法和制剂包括使用本文所述的化合物的 N- 氧化物、结晶形式（也称作多晶型物）或药学上可接受的盐，以及这些化合物的具有相同类型活性的活性代谢物。在一些情况下，化合物作为互变异构体存在。所有的互变异构体都包括在本文提出的化合物的范围内。另外，本文所述的化合物以非溶剂化的形式以及用药学上可接受的溶剂如水、乙醇等溶剂化的形式存在。本文提出的化合物的溶剂化形式也被认为在本文中公开。

[0133] 在一些实施方案中，通过在 0 到 80℃下，用诸如但不限于硫、二氧化硫、三苯基膦、硼氢化锂、硼氢化钠、三氯化磷、三溴化磷等还原剂，在诸如但不限于乙腈、乙醇、二氧杂环己烷水溶液等合适的惰性有机溶剂中处理，由相应的 N- 氧化物化合物制备出非氧化形式的本文所述的化合物。

[0134] 在一些实施方案中，将本文所述的化合物制备为前药。“前药”是指在体内被转化为母体药物的药剂。前药通常是有用的，因为在一些情况下，它们比母体药物更易于施用。在一些实施方案中，前药通过口服给药可生物利用，而母体药物则不能。在其他实施方案中，前药在药物组合物中具有比母体药物改善的溶解度。前药的一个非限制性实例是本文所述的化合物，其作为酯（“前药”）施用，以促进跨过其中水溶性对移动性不利的细胞膜的输送，但其随后一旦处于水溶性有利的细胞内部则被代谢水解成羧酸（活性实体）。前药的另一实例是与酸基团键合的短肽（聚氨基酸），其中该肽经代谢以显露活性部分。在某些实施方案中，在体内施用时，前药经化学转化为化合物的生物学、药学或治疗活性形式。在某些实施方案中，前药通过一个或多个步骤或过程经酶代谢为化合物的生物学、药学或治疗活性形式。

[0135] 为了产生前药，修饰药学活性化合物，使得该活性化合物在体内施用时将再生。在一些实施方案中，前药被设计成改变药物的代谢稳定性或转运特性、掩饰副作用或毒性、改善药物味道或改变药物的其他特性或性质。在一些实施方案中，一旦已知药学活性化合物，那么对体内的药效学过程和药物代谢的了解有助于该化合物的前药的设计（参见，例如 Nogrady(1985)Medicinal Chemistry A Biochemical Approach，Oxford University Press，New York，第 388-392 页；Silverman(1992)，The Organic Chemistry of Drug Design and Drug Action，Academic Press，Inc.，San Diego，第 352-401 页，Saulnier 等，(1994)，Bioorganic and Medicinal Chemistry Letters，Vol.4，p.1985；Rooseboom 等，Pharmacological Reviews，56：53-102，2004；Miller 等，J.Med.Chem.Vol.46，No.24，5097-5116，2003；Aesop Cho，“Recent Advances in Oral Prodrug Discovery”，Annual

Reports in Medicinal Chemistry, Vol. 41, 395-407, 2006)。

[0136] 本文所述的化合物的前药形式（其中该前药在体内代谢产生如本文所阐述的衍生物）包括在权利要求书的范围内。在一些实施方案中，一些本文描述的化合物为另一种衍生物或活性化合物的前药。

[0137] 在一些实施方案中，前药比母体药物更易于施用。在一些实施方案中，前药通过口服施给药可生物利用，而母体药物则不能。在其他实施方案中，前药在药物组合物中具有比母体药物改善的溶解度。在进一步的实施方案中，前药被设计成可逆的药物衍生物，以用作提高药物向位点特异性组织转运的调节剂。在一些实施方案中，前药的设计增加了有效水溶解度。参见，例如 Fedorak 等，Am. J. Physiol.，269：G210-218(1995)；McLoed 等，Gastroenterol，106：405-413(1994)；Hochhaus 等，Biomed. Chrom.，6：283-286(1992)；J. Larsen 和 H. Bundgaard，Int. J. Pharmaceutics，37，87(1987)；J. Larsen 等，Int. J. Pharmaceutics，47，103(1988)；Sinkula 等，J. Pharm. Sci.，64：181-210(1975)；T. Higuchi 和 V. Stella，Pro-drugsas NovelDelivery Systems，A. C. S. 学术讨论会丛刊第 14 卷；和 Edward B. Roche，Bioreversible Carriers in Drug Design，American Pharmaceutical Association and Pergamon Press，1987，此类公开内容均并入本文。

[0138] 在本文所述化合物的芳环部分上的位点易受各种代谢反应的影响，因此在芳环结构上引入适当的取代基（诸如，仅举例而言，卤素）会降低、最小化或消除这种代谢途径。

[0139] 在一些实施方案中，通过同位素（例如用放射性同位素）或通过包括但不限于使用发色团或荧光部分、生物发光标记或化学发光标记物的其他手段对本文所述的化合物进行标记。

[0140] 本文所述的化合物包括同位素标记的化合物，后者与此处提出的各通式和结构中所列举的那些相同，除了一个或多个原子被替换为具有与自然界通常发现的原子质量或质量数不同的原子质量或质量数的原子。引入本发明化合物的同位素的例子包括氢、碳、氮、氧、氟和氯的同位素，诸如，例如，分别为 ^{2}H、^{3}H、^{13}C、^{14}C、^{15}N、^{18}O、^{17}O、^{35}S、^{18}F、^{36}Cl。某些同位素标记的本文所述的化合物，例如引入了放射性同位素如 ^{3}H 和 ^{14}C 的化合物，在药物和 / 或底物组织分布试验中是有用的。此外，用同位素如氘（即 ^{2}H）替换提供了某些由更高的代谢稳定性带来的治疗优势，例如延长的体内半衰期或减少的剂量需求。

[0141] 在另外的或进一步的实施方案中，本文所述的化合物当施用到有需要的生物体时被代谢，以生成代谢物，该代谢物随后用来产生所需的效果，包括所需的治疗效果。

[0142] 在一些实施方案中，本文所述的化合物形成为和 / 或用作药学上可接受的盐。药学上可接受的盐的类型包括但不限于：(1) 酸加成盐，它们是通过使化合物的游离碱形式与药学上可接受的酸反应而形成的，所述酸包括：无机酸，例如盐酸、氢溴酸、硫酸、硝酸、磷酸、偏磷酸等；或有机酸，例如，乙酸、丙酸、己酸、环戊烷丙酸、乙醇酸、丙酮酸、乳酸、丙二酸、琥珀酸、苹果酸、马来酸、富马酸、三氟乙酸、酒石酸、柠檬酸、苯甲酸、3-(4- 羟基苯甲酰基）苯甲酸、肉桂酸、扁桃酸、甲磺酸、乙磺酸、1，2- 乙二磺酸、2- 羟基乙磺酸、苯磺酸、甲苯磺酸、2- 萘磺酸、4- 甲基双环 -[2.2.2] 辛 -2- 烯 -1- 甲酸、葡庚糖酸、4，4’- 亚甲基双 -(3- 羟基 -2- 烯 -1- 甲酸)、3- 苯基丙酸、三甲基乙酸、叔丁基乙酸、月桂基硫酸、葡糖酸、谷氨酸、羟基萘甲酸、水杨酸、硬脂酸、粘康酸、丁酸、苯乙酸、苯丁酸、丙戊酸等；(2) 当母体化合物中存在的酸性质子被置换成金属离子例如碱金属离子（例如锂、钠、钾）、碱土金属

离子（例如镁或钙）或铝离子时形成的盐。在一些实施方案中，本文所述的化合物与诸如但不限于乙醇胺、二乙醇胺、三乙醇胺、氨丁三醇、N-甲基葡糖胺、二环己基胺、三（羟甲基）甲胺的有机碱形成配合物。在其他实施方案中，本文所述的化合物与诸如但不限于精氨酸、赖氨酸等的氨基酸形成盐。用于与含有酸性质子的化合物形成盐的可接受的无机碱包括但不限于氢氧化铝、氢氧化钙、氢氧化钾、碳酸钠、氢氧化钠等。

[0143] 应当理解，提及药学上可接受的盐包括溶剂添加形式或其晶体形式，特别是溶剂化物或多晶型物。在一些实施方案中，溶剂化物含有化学计量的或非化学计量的量的溶剂，并且在结晶化过程中与药学上可接受的溶剂如水、乙醇等形成。当溶剂是水时，形成水合物，或者，当溶剂是醇时，形成醇化物。本文所述的化合物的溶剂化物在本文所述的过程中方便地制备或形成。另外，本文提供的化合物以非溶剂化的以及溶剂化的形式存在。通常，对于本文提供的化合物和方法而言，溶剂化形式被认为与非溶剂化形式是等价的。

[0144] 在一些实施方案中，本文所述的化合物处于各种形式，包括但不限于无定形形式、碾碎形式和纳米微粒形式。另外，本文所述的化合物包括结晶形式，也称作多晶型物。多晶型物包括化合物的相同元素组成的不同晶体堆积排列。多晶型物通常具有不同的X射线衍射图样、红外光谱、熔点、密度、硬度、晶形、光电性质、稳定性和溶解度。在一些实施方案中，诸如重结晶溶剂、结晶速率和储存温度等各种因素都导致单一晶型占优势。

[0145] 在其他实施方案中，药学上可接受的盐、多晶型物和/或溶剂化物的筛选和表征通过使用多种技术来完成，包括但不限于热分析、X射线衍射、光谱法、蒸汽吸附和显微术。热分析方法针对于热化学降解或热物理过程，包括但不限于多晶转变，并且此类方法用于分析多晶型之间的关系，确定重量损失，以发现玻璃化转变温度，或用于赋形剂相容性研究。此类方法包括但不限于差示扫描量热法(DSC)、调制式差示扫描量热法(MDCS)、热重量分析(TGA)以及热重量和红外分析(TG/IR)。X射线衍射法包括但不限于单晶和粉末衍射仪和同步加速器源。使用的各种光谱技术包括但不限于拉曼、FTIR、UV-VIS和NMR（液态和固态）。各种显微镜检查技术包括但不限于偏振光显微术、具有能量色散X射线分析(EDX)的扫描电子显微术(SEM)、具有EDX的环境扫描电子显微术（在气体或水蒸汽气氛中）、IR显微术和拉曼显微术。

[0146] 在整个说明书中，选择基团及其取代基以提供稳定的部分和化合物。

化合物的合成

[0147] 使用在化学文献中描述的手段、使用本文所述的方法或者通过它们的组合来完成本文所述化合物的合成。另外，本文提出的溶剂、温度和其他反应条件根据在化学文献中描述的手段、使用本文所述的方法或者通过它们的组合而不同。

[0148] 合成或从诸如但不限于Sigma-Aldrich、Fluka、Acros Organics、Alfa Aesar、Bachem等的商业来源获得用于合成本文所述化合物的起始材料和试剂。

[0149] 使用本文所述的技术和材料，并且如例如Fieser and Fieser's Reagents for Organic Synthesis，第1-17卷(John Wiley and Sons,1991)；Rodd's Chemistry of Carbon Compounds，第1-5卷及其补充(Elsevier Science Publishers,1989)；Organic Reactions，第1-40卷(John Wiley and Sons,1991)，Larock's Comprehensive Organic Transformations(VCH Publishers Inc.,1989)，March，Advanced Organic Chemistry第四版，(Wiley 1992)；Carey and Sundberg，Advanced Organic Chemistry第四版，第A和B

卷(Plenum 2000,2001)以及Green and Wuts,Protective Groups in Organic Synthesis 第三版,(Wiley 1999)(均通过引用此类公开内容而并入本文)中所述,合成本文所述化合物和具有不同取代基的其他相关化合物。为了引入在本文提供的通式中所见的各种部分,通过使用合适的试剂和条件来改进用于制备本文公开的化合物的一般方法。作为指导,使用下列合成方法。

[0150] 从可从商业来源获取的或使用本文概述的程序制备的化合物开始,合成本文所述的化合物。

[0151] 使用本文所述的反应条件,以良好的产率和纯度获得本文公开的肉桂酸异羟肟酸组合物。通过常规手段,诸如过滤、重结晶、色谱法、蒸馏及其组合,对通过本文公开的方法制备的化合物进行纯化。

[0152] 本文所提出的方案仅仅是合成本文所述化合物的一些方法的示例,而且基于该公开内容可对这些方案进行各种修改。

通过亲电体与亲核体的反应形成共价键

[0153] 本文所述的化合物使用各种亲电体或亲核体进行修饰,以形成新的官能团或取代基。标题为“共价键及其前体的实例”的表 A 列出了共价键和产生共价键的前体官能团的所选非限制性实例。表 A 用作对产生共价键的可获得的多种亲电体和亲核体组合的指导。前体官能团作为亲电子基团和亲核基团示出。

表 A :共价键及其前体的实例

共价键产物	亲电体	亲核体
羧酰胺	活化的酯	胺 / 苯胺
羧酰胺	酰基叠氮	胺 / 苯胺
羧酰胺	酰基卤	胺 / 苯胺
酯	酰基卤	醇 / 苯酚
酯	酰基腈	醇 / 苯酚
羧酰胺	酰基腈	胺 / 苯胺
亚胺	醛	胺 / 苯胺
腙	醛或酮	肼
肟	醛或酮	羟胺
烷基胺	烷基卤	胺 / 苯胺
酯	烷基卤	羧酸
硫醚	烷基卤	硫醇

醚	烷基卤	醇 / 苯酚
硫醚	烷基磺酸酯	硫醇
酯	烷基磺酸酯	羧酸
醚	烷基磺酸酯	醇 / 苯酚
酯	酐	醇 / 苯酚
羧酰胺	酐	胺 / 苯胺
苯硫酚	芳基卤	硫醇
芳胺	芳基卤	胺
硫醚	氮丙啶 (Azindine)	硫醇
硼酸酯	硼酸酯	甘醇

羧酰胺	羧酸	胺 / 苯胺
酯	羧酸	醇
肼	酰肼	羧酸
N- 酰基脲或酐	碳二亚胺	羧酸
酯	重氮烷	羧酸
硫醚	环氧化物	硫醇
硫醚	卤代乙酰胺	硫醇
三嗪胺	卤代三嗪	胺 / 苯胺
三嗪基醚	卤代三嗪	醇 / 苯酚
脒	亚胺酯	胺 / 苯胺
脲	异氰酸酯	胺 / 苯胺
氨基甲酸酯	异氰酸酯	醇 / 苯酚
硫脲	异硫氰酸酯	胺 / 苯胺
硫醚	马来酰亚胺	硫醇

亚磷酸酯	亚磷酰胺	醇
甲硅烷基醚	甲硅烷基卤	醇
烷基胺	磺酸酯	胺 / 苯胺
硫醚	磺酸酯	硫醇
酯	磺酸酯	羧酸
醚	磺酸酯	醇
磺酰胺	磺酰基卤	胺 / 苯胺
磺酸酯	磺酰基卤	苯酚 / 醇

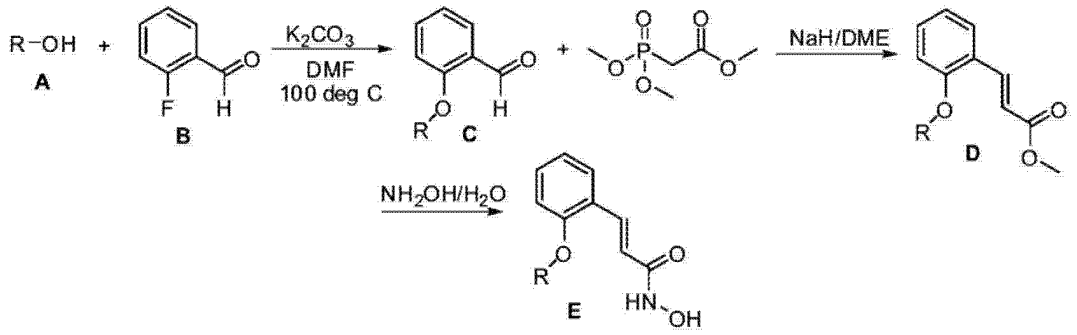
[0154] 在所述的反应中，在某些情况下必须保护反应性官能团，例如羟基、氨基、亚氨基、硫代或羧基（在这些官能团是终产物中所需的情况下），以避免它们不必要地参与反应。保护基团用来封闭一些或全部的反应性部分，并阻止这类基团参与化学反应，直至该保护基团被去除。在一个实施方案中，各个保护基团可通过不同的手段去除。保护基团以及适用于保护基团的产生和去除的技术的详细说明在通过引用此类公开内容而并入本文的 Greene 和 Wuts，Protective Groups in Organic Synthesis，第三版，John Wiley&Sons，New York，NY，1999 和 Kocienski，Protective Groups，Thieme Verlag，New York，NY，1994 中进行了描述。

一般合成

肉桂酸羟基酰胺化合物

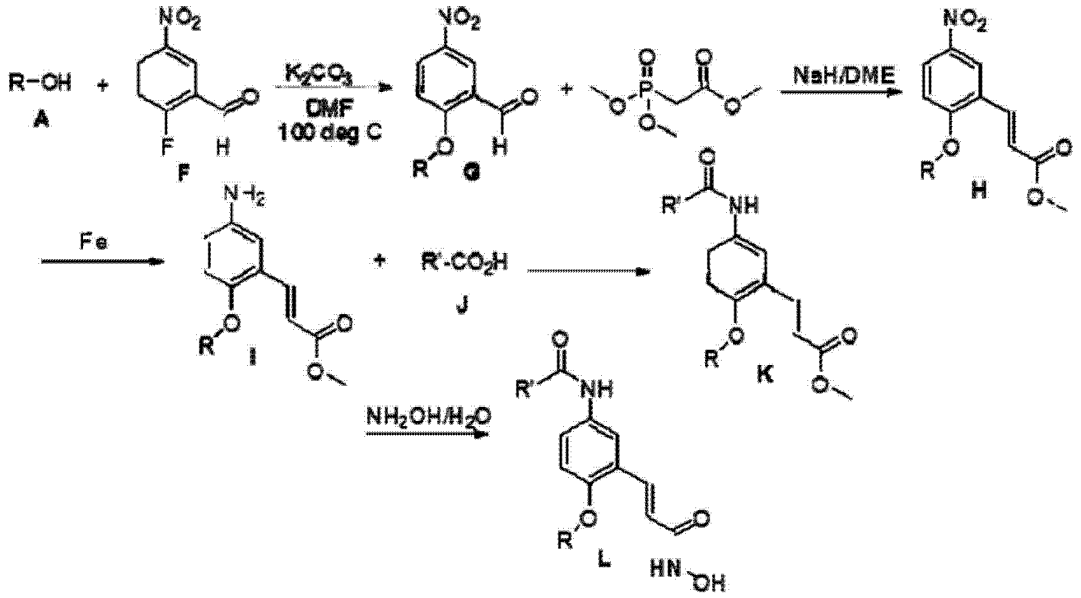
[0155] 本文所述的肉桂酸羟基酰胺化合物从市售材料进行制备。

合成路线 I：



[0156] 具有化合物 E 的结构的肉桂酸羟基酰胺化合物通常可使用以上所示的合成路线 I 进行合成。通常，化合物 A 的醇（其中 R 是例如但不限于芳基、杂芳基或 C_2-C_{10} 杂环烷基）与化合物 B 的取代的苯甲醛反应以形成具有结构 C 的化合物。化合物 C 与膦酰基乙酸三甲酯反应得到具有结构 D 的化合物。化合物 D 与 50％羟胺溶液反应得到具有结构 E 的化合物。

合成路线 II：



[0157] 具有化合物 L 的结构的肉桂酸羟基酰胺化合物通常可使用以上所示的合成路线 II 进行合成。通常，化合物 A 的醇（其中 R 是例如但不限于芳基、杂芳基或 C_2-C_{10} 杂环烷基）与化合物 F 的硝基取代的苯甲醛反应以形成具有结构 G 的化合物。化合物 G 与膦酰基乙酸三甲酯反应得到具有结构 H 的化合物。硝基与 Fe 的还原反应提供了具有结构 I 的化合物。羧酸化合物 J 与具有结构 I 的化合物反应提供了具有结构 K 的化合物。化合物 K 与 50％羟胺溶液反应得到具有结构 L 的化合物。

[0158] 在整个说明书中，选择基团及其取代基以提供稳定的部分和化合物。

某些术语

[0159] 应当理解，前面的一般性描述和下面的详细描述仅是示例性的和说明性的，并不是对所请求保护的任何主题的限制。在本申请中，除非另有特别说明，单数形式的使用包括复数形式。必须注意，除非上下文另有明确说明，本说明书和所附的权利要求书中使用的单数形式“一个”、“一种”和“该”包括复数形式的指示物。在本申请中，除非另有说明，“或”的使用意为“和 / 或”。此外，术语“包括”以及其他形式如“包含”、“含有”和“具有”的使用不是限制性的。

[0160] 标准化学术语的定义可在文献著作中找到，包括 Carey 和 Sundberg 的“Advanced Organic Chemistry 第四版”A 卷 (2000) 和 B 卷 (2001)，Plenum Press，NewYork。除非另有说明，否则使用质谱法、NMR、HPLC、蛋白质化学、生物化学、重组 DNA 技术和药理学的常规方法。另外，HDAC8 的核酸和氨基酸序列在例如美国专利 6,875,598 中公开。除非提供具体的定义，否则与本文描述的分析化学、有机合成化学以及医学和药物化学关联使用的命名及其实验室程序和技术是本领域已知的。标准技术用于化学合成、化学分析、药物制备、配制和递送以及患者的治疗。标准技术用于重组 DNA、寡核苷酸合成以及组织培养和转化（例如电穿孔、脂质转染）。例如，使用制造商的试剂盒的说明书或如本文所述的，来实施反应和纯化技术。前述的技术和程序通常通过常规方法以及如本说明书通篇所引用和讨论的各种一般的和更具体的参考文献中所述的那样来进行。

[0161] 应当理解，本文描述的方法和组合物不限于本文描述的具体方法、方案、细胞系、构建体和试剂，而本身可变化。还应当理解，本文所用的术语仅仅是出于描述特定实施方案

的目的，并非意图限制本文描述的方法、化合物、组合物的范围。

[0162] 如本文所用的，C_1-C_x 包含 C_1-C_2、C_1-C_3. . . C_1-C_x。C_1-C_x 是指构成其指定部分（不包括任选的取代基）的碳原子的数目。

[0163] “烷基”基团是指脂肪族烃基。在一些实施方案中，烷基部分是“饱和的烷基”基团，这意味着其不含有任何烯烃或炔烃部分。在其他实施方案中，烷基部分是“不饱和的烷基”部分，这意味着其含有至少一个烯烃或炔烃部分。“烯烃”部分是指由至少两个碳原子和至少一个碳碳双键组成的基团，而“炔烃”部分是指由至少两个碳原子和至少一个碳碳叁键组成的基团。烷基部分，不管是饱和的还是不饱和的，是支链、直链或环状的。

[0164] “烷基”部分具有 1 至 10 个碳原子（每当在本文中出现时，数值范围如“1 至 10”是指给定范围内的各个整数；例如，“1 至 10 个碳原子”意指该烷基由 1 个碳原子、2 个碳原子、3 个碳原子等等，直到 10 个碳原子并且包括 10 个碳原子组成，虽然本定义也涵盖未指定数值范围的术语“烷基”的存在）。本文所述的化合物的烷基被指定为“C_1-C_6 烷基”或类似的指定。仅举例来说，“C_1-C_6 烷基”表示在烷基链中有 1-6 个碳原子，即该烷基链选自甲基、乙基、丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、戊基、异戊基、新戊基和己基。典型的烷基包括但绝不限于甲基、乙基、丙基、异丙基、丁基、异丁基、叔丁基、戊基、己基、乙烯基、丙烯基、丁烯基、环丙基、环丁基、环戊基、环己基等。在一些实施方案中，烷基是取代的或未取代的。取决于结构，烷基是单价基团或双价基团（即亚烷基）。

[0165] “烷氧基”是指（烷基）O- 基团，其中烷基如本文所定义。烷氧基的实例包括但不限于，甲氧基、乙氧基、丙氧基、异丙氧基、丁氧基、环丙氧基、环戊氧基、环己氧基等。

[0166] “羟烷基”是指被羟基取代的烷基。

[0167] “羟基烷氧基”是指被羟基取代的烷氧基。

[0168] “羟烷基氨基烷氧基”是指被氨基取代的烷氧基，该氨基被如本文所定义的羟烷基所取代。

[0169] “烷氧基烷基”是指被烷氧基取代的烷基。

[0170] “烷氧基烷基氧基”是指被如本文所定义的烷氧基取代的如本文所定义的烷氧基。

[0171] “烷氧基羰基”是指 -C(=O)O-（烷基）基团，其中烷基如本文所定义。烷氧基羰基的非限制性实例包括，例如甲氧基羰基、乙氧基羰基等。

[0172] “烷氧基羰基氨基”是指 -NR(C=O)-O-（烷基），其中烷基如本文所定义且 R 是 H、烷基、杂烷基、卤代烷基等。

[0173] 术语“烯基”是指一类烷基，其中该烷基的前两个原子形成双键，该双键不是芳香基团的一部分。即，烯基始于原子 -C(R)=CR_2，其中 R 是指该烯基的其余部分，它们是相同的或不同的。烯基的非限制性实例包括 -CH=CH_2、-C(CH_3)=CH_2、-CH=$CHCH_3$ 和 -C(CH_3)=$CHCH_3$。烯基部分是支链、直链或环状的（在该情况下，它也可被称作“环烯基”）。烯基具有 2-6 个碳原子。在一些实施方案中，烯基是取代的或未取代的。取决于结构，烯基是单价基团或双价基团（即亚烯基）。

[0174] “烯基羰基”是指 -C(O)-（烯基）基团，其中烯基如本文所定义。

[0175] “烯基羰基氧基”是指 -OC(O)-（烯基）基团，其中烯基如本文所定义。

[0176] “烯基氧基”是指 -O-（烯基）基团，其中烯基如本文所定义。

[0177] 术语“炔基”是指一类烷基，其中该烷基的前两个原子形成叁键。即，炔

基始于原子 -C ≡ C-R，其中 R 是指该炔基的其余部分。炔基的非限制性实例包括 -C ≡ CH、-C ≡ CCH_3、-C ≡ CCH_2CH_3 和 -C ≡ $CCH_2CH_2CH_3$。炔基部分的“R”部分是支链、直链或环状的。在一些实施方案中，炔基具有 2-6 个碳原子。在其他实施方案中，炔基是取代的或未取代的。取决于结构，炔基是单价基团或双价基团（即亚炔基）。

[0178] “氨基”或“胺”是指 $-NH_2$ 基团、N- 氧化物衍生物、脂肪胺或芳香胺。脂肪胺类包括：伯胺，其中一个氢原子被有机取代基代替；仲胺，其中两个氢原子被两个有机取代基代替；以及叔胺，其中在 N 原子上的全部三个取代基是有机取代基。

[0179] 术语“烷基胺”或“烷基氨基”是指 $-N(烷基)_xH_y$ 基团，其中烷基如本文所定义且 x 和 y 选自 x = 1、y = 1 和 x = 2、y = 0。当 x = 2 时，烷基与它们所连接的氮一起任选地形成环状环系。术语“烷基胺”也指被烷基取代的氨基。“二烷基氨基”是指 $-N(烷基)_2$ 基团，其中烷基如本文所定义。

[0180] “氨基烷基”是指被氨基取代的如本文所定义的烷基。

[0181] “氨基烷氧基”是指被氨基取代的烷氧基。

[0182] “氨基羰基”是指 $-CONH_2$ 基团。

[0183] “氨基磺酰基”意指 $-S(O)_2NH_2$ 基团。

[0184] 术语“烷基氨基烷基”是指被如本文定义的烷基胺取代的如本文定义的烷基。“二烷基氨基烷基”是指被二烷基氨基取代的烷基。

[0185] “烷基氨基烷氧基”是指被烷基胺取代的烷氧基。

[0186] “烷基氨基羰基”意指 -C(O)R 基团，其中 R 是如本文定义的烷基氨基。

[0187] “烷基氨基羰基氨基”是指 -NHC(=O)-(烷基氨基)。

[0188] “烷基氨基羰基氧基”是指 -OC(=O)-(烷基氨基)。

[0189] “烷基氨基磺酰基”是指 $-S(=O)_2NHR$ 基团，其中 R 是如本文所定义的烷基。

[0190] “烷基羰基”意指 -C(=O)R 基团，其中 R 是如本文定义的烷基。

[0191] “烷基羰基氨基”意指 -NR’C(=O)-(烷基)，其中 R’是氢、烷基、卤代烷基、杂烷基。

[0192] “烷基羰基氧基”意指 -OC(=O)R 基团，其中 R 是如本文所定义的烷基。

[0193] “二烷基氨基烷基氧基”是指被二烷基氨基取代的烷氧基。

[0194] “二烷基氨基羰基”是指 -C(=O)R，其中 R 是二烷基氨基。

[0195] “二烷基氨基羰基氨基”是指 -NR’-C(=O)-(二烷基氨基)，其中 R’是氢、烷基、杂烷基、卤代烷基以及如本文所定义的二烷基氨基羰基。

[0196] “二烷基氨基羰基氧基”是指 -O(C=O)-(二烷基氨基)，二烷基氨基羰基如本文所定义。

[0197] “二烷基氨基磺酰基”是指 $-S(O)_2NR_2$，其中 R 是如本文定义的烷基。

[0198] 如本文所用的术语“环”是指任意的共价闭合的结构。环包括例如碳环（例如芳基和环烷基）、杂环（例如杂芳基和非芳香族杂环）、芳环（例如芳基和杂芳基）和非芳环（例如环烷基和非芳香族杂环）。在一些实施方案中，环任选地被取代。在其他实施方案中，环是单环或多环。

[0199] 术语“... 元环”是指任意环状结构。术语“元”意在表示构成环的骨架原子的数目。因此，例如，环己基、苯基、吡啶、哌啶、吗啉、哌嗪、哒嗪、嘧啶、吡嗪、吡喃和噻喃是 6 元

环，而环戊基、吡咯烷、咪唑、噁唑、噻唑、吡咯、呋喃和噻吩是 5 元环。

[0200] 术语“碳环的”或“碳环”是指其中构成环的每个原子都是碳原子的环。碳环包括芳基和环烷基。该术语因而区分了碳环和杂环（“杂环的”），杂环中的环骨架含有至少一个不是碳的原子（即杂原子）。杂环包括杂芳基和杂环烷基。在一些实施方案中，碳环和杂环任选地被取代。

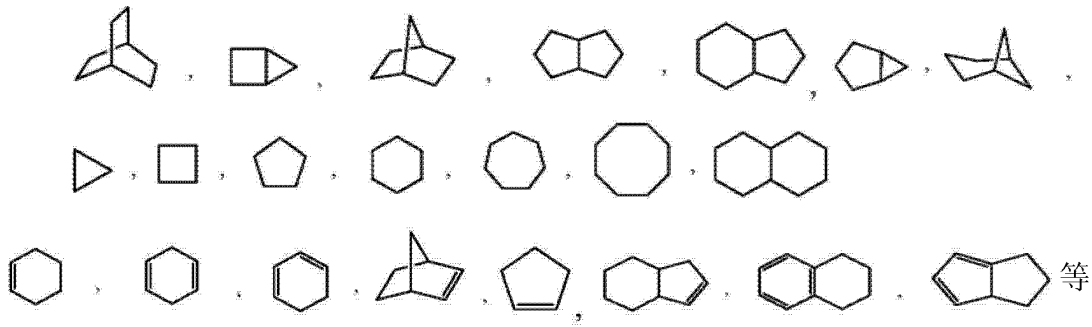
[0201] 术语“芳香族”是指具有包含 4n+2 个 π 电子的离域 π 电子体系的平面环，其中 n 是整数。在一些实施方案中，芳环由五、六、七、八、九个或超过九个原子构成。在其他实施方案中，芳环任选地被取代。术语“芳香族”既包括碳环芳基（“芳基”，例如苯基）也包括杂环芳基（或“杂芳基”或“芳杂环”）基团（例如吡啶）。该术语包括单环或稠环多环（即共用相邻碳原子对的环）基团。

[0202] 如本文所用的术语“芳基”是指其中构成环的每个原子都是碳原子的芳环。在一些实施方案中，芳基环由五、六、七、八、九、十个或超过十个碳原子构成。在一些实施方案中，芳基任选地被取代。在一些实施方案中，芳基是 C_6-C_{10} 芳基。芳基的实例包括但不限于苯基和萘基。在一个方面，芳基是苯基。取决于结构，芳基是单价基团或双价基团（即亚芳基）。

[0203] “芳烷基”或“芳基烷基”是指被如本文所定义的芳基取代的如本文所定义的烷基。

[0204] “苯基烷基”是指被苯基取代的烷基。

[0205] 术语“环烷基”是指单环的或多环的非芳香族基团，其中构成环的每个原子（即骨架原子）都是碳原子。环烷基是饱和的或部分不饱和的。在一些实施方案中，环烷基与芳香环稠合。环烷基包括具有 3-10 个环原子的基团。环烷基的说明性实例包括但不限于以下基团：



等。环烷基包括但不限于环丙基、环丁基、环戊基、环己基、环庚基和环辛基。在一个方面，环烷基是 C_3-C_6 环烷基。

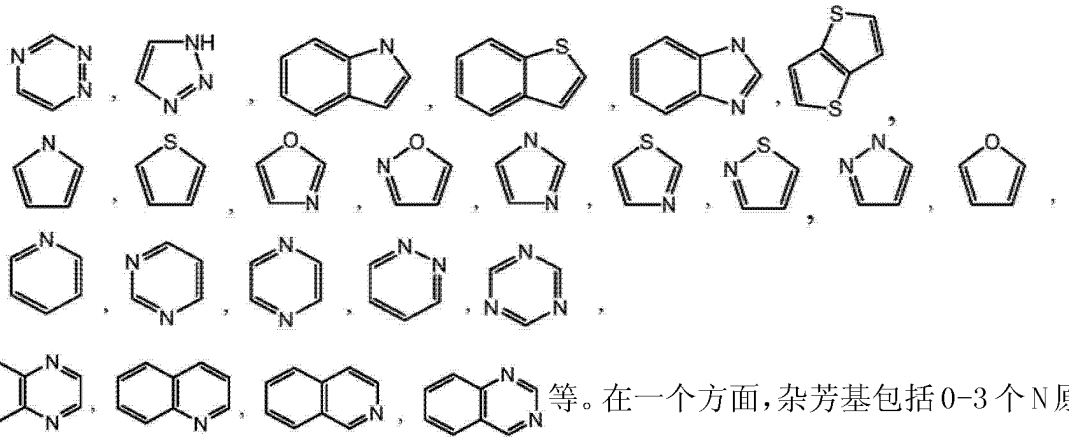
[0206] “环烷基烷基”是指被如本文所定义的环烷基取代的如本文所定义的烷基。

[0207] “环烷基羰基”是指 -C(= O)- 环烷基。

[0208] 术语“杂环”是指含有 1-4 个各自选自 O、S 和 N 的环杂原子的芳香杂环和杂脂环基团，其中各个杂环基团在其环系中具有 4-10 个原子，且条件是所述基团的环不包含两个相邻的 O 或 S 原子。非芳香族杂环基团包括在其环系中含有 3 个原子的基团，而芳香族杂环基团在其环系中必须含有至少 5 个原子。杂环基团包括苯并稠合的环系。3 元杂环基团的一个实例是吖丙啶基（衍生自氮丙啶）。4 元杂环基团的一个实例是氮杂环丁烷基（衍生自氮杂环丁烷）。5 元杂环基团的一个实例是噻唑基。6 元杂环基团的一个实例是吡啶基，而 10 元杂环基团的一个实例是喹啉基。非芳香族杂环基团的实例是吡咯烷基、四氢呋喃基、

二氢呋喃基、四氢噻吩基、四氢吡喃基、二氢吡喃基、四氢噻喃基、哌啶子基、吗啉基、硫代吗啉基、噻噁烷基、哌嗪基、吖丙啶基、氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、高哌啶基、氧杂环庚烷基、硫杂环庚烷基、氧氮杂䓬基、二氮杂䓬基、硫氮杂䓬基、1,2,3,6- 四氢吡啶基、2- 吡咯啉基、3- 吡咯啉基、二氢吲哚基、2H- 吡喃基、4H- 吡喃基、二氧杂环己烷基、1,3- 二氧杂环戊烷基、吡唑啉基、二噻烷基、二硫杂环戊烷基、二氢吡喃基、二氢噻吩基、二氢呋喃基、吡唑烷基、咪唑啉基、咪唑烷基、3- 氮杂双环 [3.1.0] 己烷基、3- 氮杂双环 [4.1.0] 庚烷基、3H- 吲哚基和喹嗪基。芳香族杂环基团的实例是吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、萘啶基和呋喃并吡啶基。前述基团在可能的情况下是 C- 连接的或 N- 连接的。例如，由吡咯衍生的基团被命名为吡咯 -1- 基 (N- 连接的）或吡咯 -3- 基 (C- 连接的）。此外，由咪唑衍生的基团被命名为咪唑 -1- 基或咪唑 -3- 基（均为 N- 连接的）或咪唑 -2- 基、咪唑 -4- 基或咪唑 -5- 基（均为 C- 连接的）。杂环基团包括苯并稠合的环系和被一个或两个氧代（＝ O) 部分取代的环系，例如吡咯烷 -2- 酮。

[0209] 术语“杂芳基”或者“芳香杂环”是指包含一个或多个选自氮、氧和硫的环杂原子的芳基基团。包含 N 的“芳香杂环”或“杂芳基”部分是指其中环上的至少一个骨架原子是氮原子的芳香族基团。多环杂芳基是稠合的或非稠合的。杂芳基的说明性实例包括以下基团：



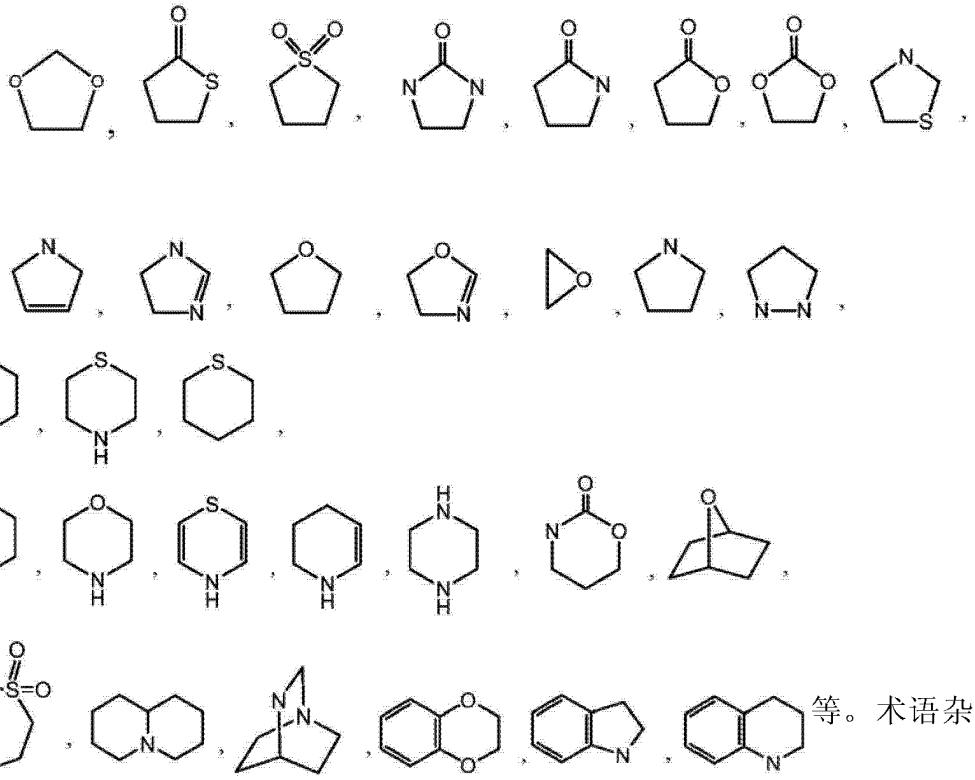
等。在一个方面，杂芳基包括 0-3 个 N 原子。在一个方面，杂芳基包括 1-3 个 N 原子。在一个方面，杂芳基包括 0-3 个 N 原子、0-1 个 O 原子和 0-1 个 S 原子。在一个方面，杂芳基是单环的或双环的杂芳基。在一个方面，杂芳基是单环杂芳基。在一个方面，杂芳基是 C_1-C_{10} 杂芳基。在另一方面，杂芳基是 C_2-C_9 杂芳基。在一个方面，单环杂芳基是 C_1-C_5 杂芳基。在一个方面，双环杂芳基是 C_5-C_{10} 杂芳基。取决于结构，杂芳基可以是单价基团或双价基团（即亚杂芳基）。

[0210] 在一些实施方案中，取代或未取代的杂芳基选自吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、4- 氮杂吲哚基、5- 氮杂吲哚基、6- 氮杂吲哚基、7- 氮杂吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑

基、喹唑啉基、喹喔啉基、咪唑并 [1,2-a] 吡啶基、噻吩并吡啶基和呋喃并吡啶基。在其他实施方案中，取代或未取代的杂芳基选自吡啶基、嘧啶基、吡嗪基、喹啉基、异喹啉基、吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、异吲哚基、蝶啶基、嘌呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、萘啶基、咪唑并 [1,2-a] 吡啶基、噻吩并吡啶基和呋喃并吡啶基。在另外其他的实施方案中，取代或未取代的杂芳基选自吡啶基、嘧啶基、吡嗪基、喹啉基、异喹啉基、哒嗪基、喹唑啉基、喹喔啉基。在再其他的实施方案中，取代或未取代的杂芳基选自吡啶基和喹啉基。

[0211] “杂芳烷基”或“杂芳基烷基”是指被如本文定义的杂芳基取代的如本文定义的烷基。

[0212] “杂脂环基”或“杂环烷基”是指其中至少一个骨架环原子是选自氮、氧和硫的杂原子的环烷基。该基团与芳基或杂芳基稠合。杂环烷基（亦被称为非芳香族杂环基）的说明性实例包括：



等。术语杂脂环还包括碳水化合物的所有环形式，包括但不限于单糖、二糖和寡糖。除非另有说明，杂环烷基在环上具有 2 至 10 个碳原子。应当理解，当提到杂环烷基上的碳原子数时，杂环烷基上的碳原子数与构成杂环烷基（即杂环烷基环的骨架原子）的原子（包括杂原子）的总数是不相同的。在一个方面，杂环烷基是 C_2-C_{10} 杂环烷基。在另一方面，杂环烷基是 C_4-C_{10} 杂环烷基。

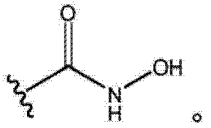
[0213] 在一些实施方案中，取代或未取代的杂环烷基选自喹噁基、二氧杂环己烯基、哌啶基、吗啉基、硫代吗啉基、噻噁基、四氢吡啶基、哌嗪基、噁噁烷酮基、二氢吡咯基、二氢咪唑基、四氢呋喃基、四氢吡喃基、二氢噁唑基、环氧乙烷基、吡咯烷基、吡唑烷基、二氢噻吩基、咪唑烷酮基、吡咯烷酮基、二氢呋喃酮基、二氧杂环戊烷酮基、噻唑烷基、哌啶酮基、二氢吲哚基、四氢喹啉基、四氢异喹啉基和四氢噻吩基。在其他实施方案中，取代或未取代的杂环

烷基选自哌啶基、吗啉基、哌嗪基、二氢吡咯基、二氢咪唑基、四氢呋喃基、二氢噁唑基、吡咯烷基、吡唑烷基、二氢噻吩基、咪唑烷酮基、吡咯烷酮基、哌啶酮基、二氢吲哚基、四氢喹啉基、四氢异喹啉基和四氢噻吩基。在另外其他的实施方案中，取代或未取代的杂环烷基选自哌啶基、吗啉基、哌嗪基、四氢呋喃基、吡咯烷基、吡咯烷酮基、哌啶酮基、二氢吲哚基、四氢喹啉基和四氢噻吩基。在一些实施方案中，取代或未取代的杂环烷基选自哌啶基、吗啉基、硫代吗啉基、哌嗪基和吡咯烷基。

[0214] “杂环烷基烷基”是指被如本文定义的杂环烷基取代的如本文定义的烷基。

[0215] “杂环烷基烷氧基”是指被如本文所定义的杂环烷基取代的如本文所定义的烷氧基，其中杂环烷基包括烷基取代基。

[0216] “异羟肟酸”、“氧肟酸”、“N- 羟基甲酰胺”或“羧酸羟基酰胺”是指：



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[0217] 术语“卤代”或者“卤素”意指氟代、氯代、溴代和碘代。

[0218] 术语“卤代烷基”、“卤代烯基”、“卤代炔基”和“卤代烷氧基”包括被一个或多个卤素取代的烷基、烯基、炔基和烷氧基结构。在一些实施方案中，卤素是相同或不同的。术语“氟烷基”和“氟氧烷基”分别包括卤代烷基和卤代烷氧基，其中卤素是氟。卤代烷基的非限制性实例包括 $-CH_2Cl$、$-CF_3$、$-CHF_2$、$-CH_2CF_3$、$-CF_2CF_3$、$-CF(CH_3)_3$ 等。氟烷基的非限制性实例包括 $-CF_3$、$-CHF_2$、$-CH_2F$、$-CH_2CF_3$、$-CF_2CF_3$、$-CF_2CF_2CF_3$、$-CF(CH_3)_3$ 等。卤代烷氧基的非限制性实例包括 $-OCF_3$、$-OCHF_2$、$-OCH_2F$、$-OCH_2CF_3$、$-OCF_2CF_3$、$-OCF_2CF_2CF_3$、$-OCF(CH_3)_3$ 等。

[0219] 术语“杂烷基”、“杂烯基”和“杂炔基”包括任选取代的烷基、烯基和炔基基团并且具有选自除碳以外的原子例如氧、氮、硫、磷、硅或其组合的一个或多个骨架链原子。杂原子位于杂烷基的任意位置。在一些实施方案中，多达两个杂原子是连续的，例如，举例而言，$-CH_2-NH-OCH_3$ 和 $-CH_2-O-Si(CH_3)_3$。除杂原子数外，“杂烷基”包含 1 至 6 个碳原子，“杂烯基”包含 2 至 6 个碳原子，而“杂炔基”包含 2 至 6 个碳原子。

[0220] 术语“部分”是指分子的特定区段或官能团。化学部分通常被认为是嵌入分子中或附加在分子上的化学实体。

[0221] “氰基烷基氨基羰基”是指 $-C(=O)NR'$（氰基烷基）基团，其中 R' 是如本文所定义的氢、烷基、杂烷基、卤代烷基；氰基烷基如本文所定义。

[0222] “异硫氰酸基”是指 -NCS 基团。

[0223] “烷硫基”意指 -SR 基团，其中 R 是如本文定义的烷基。

[0224] “酰基氨基”是指 $RC(=O)N(R')-$，其中 R' 是氢、羟基、烷基或烷氧基。在一些实施方案中，R' 是 H 或 R。

[0225] “烷基亚磺酰基”意指 $-S(O)R$，其中 R 是如本文定义的烷基。

[0226] “烷基磺酰基”意指 $-SO_2R$，其中 R 是如本文定义的烷基。

[0227] “烷基磺酰基氨基”意指 $-N(R')SO_2R$，其中 R 是如本文所定义的氢、烷基、杂烷基、卤代烷基；且 R 是如本文所定义的烷基。

[0228] “苯基磺酰基”意指 $-S(=O)_2-$ 苯基部分。

[0229] “苯基磺酰基氨基”是指 $-NR'SO_2-$（苯基），其中 R' 是如本文所定义的氢、烷基、杂

烷基、卤代烷基。

[0230] “杂芳基氨基羰基”是指 -C(= O)NR’（杂烷基）基团，其中 R’ 是如本文所定义的氢、烷基、杂烷基、卤代烷基；且杂烷基如本文所定义。

[0231] “芳基氨基羰基”是指 -C(= O)NR’（芳基）基团，其中 R’ 是如本文定义的氢、烷基、杂烷基、卤代烷基；且芳基如本文所定义。

[0232] “芳基羰基氨基”是指 -NR’C(= O)-（芳基）基团，其中 R’ 是如本文定义的氢、烷基、杂烷基、卤代烷基；且芳基如本文所定义。

[0233] 如本文所用的取代基“R”，当单独出现且没有指定数目时，是指选自烷基、卤代烷基、杂烷基、烯基、环烷基、环烷基烷基、芳基、芳基烷基、杂芳基（通过环上的碳键合）、杂芳基烷基、杂环烷基和杂环烷基烷基的取代基。

[0234] 术语“任选取代的”或“取代的”意思是所提及的基团被一个或多个另外的基团取代，这些另外的基团分别且独立地选自烷基、环烷基、芳基、杂芳基、杂环烷基、羟基、烷氧基、芳氧基、烷硫基、芳硫基、烷基亚砜、芳基亚砜、烷基砜、芳基砜、氰基、卤代、酰基、酰氧基、异氰酸基、硫氰酸基、异硫氰酸基、硝基、卤代烷基、氟烷基和氨基（包括单取代和二取代的氨基（即 $-NH_2$、-NHR、$-N(R)_2$））及其受保护的衍生物。举例来说，任选的取代基是 L^sR^s，其中各个 L^s 独立地选自键、-O-、-C(= O)-、-S-、-S(= O)-、-S(= $O)_2$-、-NH-、-NHC(O)-、-C(O)NH-、S(= $O)_2$NH-、-NHS(= $O)_2$、-OC(O)NH-、-NHC(O)O-、-(C_1-C_6 烷基）-或 -(C_2-C_6 烯基）-；并且各个 R^s 独立地选自 H、(C_1-C_6 烷基）、(C_3-C_8 环烷基）、芳基、杂芳基、杂环烷基和 C_1-C_6 杂烷基。在一个方面，取代的基团被一个或多个选自卤素、-OH、-OC_1-C_4 烷基、C_1-C_4 烷基、C_1-C_4 杂烷基、C_1-C_4 氟烷基和 -OC_1-C_4 氟烷基的取代基所取代。在又一其他方面，取代的基团被一个或多个选自 F、Cl、Br、-OH、-OCH_3、-CH_3 和 -CF_3 的取代基所取代。在另外其他的实施方案中，取代的基团被一个或多个选自 F、Cl 和 Br 的取代基所取代。在一个方面，取代的基团被前述基团之一取代。形成上述取代基的保护性衍生物的保护基团可见于诸如上述 Greene 和 Wuts 的参考文献。

[0235] 本文所述的化合物具有一个或多个立构中心，并且各个中心以 R 或 S 构型存在。本文提出的化合物包括所有非对映异构、对映异构和差向异构形式，及其适当的混合物。如果需要的话，通过用手性色谱柱分离立体异构体来获得立体异构体。

[0236] 本文所述的方法和制剂包括使用具有式 I 结构的化合物的 N- 氧化物、结晶形式（也称作多晶型物）或药学上可接受的盐，以及这些化合物的具有相同类型活性的活性代谢物。在一些情况下，化合物作为互变异构体存在。所有的互变异构体都包括在本文提出的化合物的范围内。另外，本文所述的化合物以非溶剂化的形式存在，以及以用药学上可接受的溶剂如水、乙醇等溶剂化的形式存在。本文提出的化合物的溶剂化形式也被认为在本文中公开。

[0237] 术语“试剂盒”和“制品”作为同义词使用。

[0238] 术语“受试者”或“患者”包括哺乳动物和非哺乳动物。哺乳动物的实例包括但不限于哺乳动物纲的任何成员：人、非人灵长类动物，如黑猩猩，以及其他猿类和猴物种；农畜，如牛、马、绵羊、山羊、猪；家畜，如兔、狗和猫；实验室动物，包括啮齿动物，如大鼠、小鼠和豚鼠，等等。非哺乳动物的实例包括但不限于鸟类、鱼等。在本文提供的方法和组合物的一个实施方案中，哺乳动物是人类。

[0239] 本文使用的术语“治疗”包括预防性地和/或治疗性地减轻、缓和或改善疾病或状况的症状，预防额外的症状，改善或预防症状的潜在原因，抑制疾病或状况，例如阻止疾病或状况的发展、缓解疾病或状况、使疾病或状况消退、缓解疾病或状况引起的状况，或者停止疾病或状况的症状。

[0240] 本文使用的“选择性 HDAC8 抑制剂”是指这样一种化合物：其对于抑制 HDAC8 脱乙酰酶活性的 IC_{50} 比对于抑制另一种 HDAC 的脱乙酰酶活性的 IC_{50} 低至少约 5 倍至超过 500 倍。在一些实施方案中，该选择性 HDAC8 抑制剂对于抑制 HDAC8 脱乙酰酶活性的 IC_{50} 比对于抑制另一种 HDAC 的脱乙酰酶活性的 IC_{50} 低约 5、约 10、约 50、约 100、约 150、约 200、约 250、约 300、约 350、约 400、约 450 或超过约 500 倍。在一些实施方案中，该选择性 HDAC8 抑制剂对于抑制 HDAC8 脱乙酰酶活性的 IC_{50} 比对于抑制 HDAC1、HDAC2、HDAC3、HDAC6、HDAC10 和 HDAC11 中的至少一种（在另一实施方案中，HDAC1、HDAC2、HDAC3、HDAC6、HDAC10 和 HDAC11 中的至少两种；在另一实施方案中，全部 HDAC1、HDAC2、HDAC3、HDAC6、HDAC10 和 HDAC11）的脱乙酰酶活性的 IC_{50} 低至少约 10 倍。在另一实施方案中，该选择性 HDAC8 抑制剂针对 HDAC8 脱乙酰酶活性的 IC_{50} 比对于抑制 HDAC1、HDAC2、HDAC3、HDAC6、HDAC10 和 HDAC11 中的至少一种（在另一实施方案中，HDAC1、HDAC2、HDAC3、HDAC6、HDAC10 和 HDAC11 中的至少两种；在另一实施方案中，全部 HDAC1、HDAC2、HDAC3、HDAC6、HDAC10 和 HDAC11）的脱乙酰酶活性的 IC_{50} 低至少约 20 倍。

[0241] 如本文使用的，通过施用特定化合物或药物组合物导致的特定疾病、病症或状况的症状的改善，是指归因于该化合物或组合物的施用或与其施用相关的任何严重程度的减轻、发作的延迟、进展的减缓或持续时间的缩短，不管是永久的还是暂时的，持续的还是瞬时的。

[0242] 本文使用的术语 HDAC 的“抑制”或“抑制剂”是指对组蛋白脱乙酰酶活性的抑制。

[0243] 本文中针对制剂、组合物或成分使用的术语“可接受的”意思是对被治疗的受试者的一般健康状况没有持续的不利影响。

[0244] 本文使用的“药学上可接受的”是指诸如载体或稀释剂等材料，其不消除化合物的生物活性或性质，并且相对无毒，即该材料施用于个体而不引起不期望的生物效应，或不以有害的方式与含有它的组合物的任何成分相互作用。

[0245] 术语“药物组合物”是指本文所述化合物与其他化学成分如载体、稳定剂、稀释剂、分散剂、悬浮剂、增稠剂和/或赋形剂的混合物。该药物组合物有助于化合物对生物体的施用。施用化合物的多种技术包括但不限于：静脉内、口服、气雾剂、肠胃外、眼、肺和局部给药。

[0246] 本文使用的术语“有效量”或“治疗有效量”是指所施用的药剂或化合物的足够量，该量会在一定程度上减轻所治疗的疾病或状况的一种或多种症状。结果是疾病的体征、症状或起因的减少和/或减轻，或者生物系统的任何其他期望的变化。例如，用于治疗用途的“有效量”是包含如本文公开的 HDAC8 抑制化合物的组合物的量，该量是提供疾病症状的临床上显著的下降所需要的。在任意单独的情况下，适当的“有效量”使用例如剂量递增研究等技术来确定。

[0247] 本文所用的术语“增强”意指在效力上或在持续时间上增加或延长所需的效果。因此，关于增强治疗剂的效果，术语“增强”是指在效力上或在持续时间上增加或延长其他治

疗剂对系统的效果的能力。本文所用的“增强有效量”是指足以增强另一种治疗剂在期望的系统中的效果的量。

[0248] 本文所用的术语“共同施用”或类似用语意在涵盖对一名患者施用选定的多种治疗剂，而且意在包括通过相同或不同的给药途径或者在相同或不同的时间施用该药剂的治疗方案。

[0249] 本文所用的术语“载体”是指有助于将化合物引入细胞或组织中的相对无毒的化学化合物或试剂。

[0250] 术语“稀释剂”是指用于在递送前稀释目标化合物的化学化合物。稀释剂因其提供更稳定的环境而也用于稳定化合物。使用溶解在缓冲溶液（其也提供pH的控制或维持）中的盐，包括但不限于磷酸盐缓冲盐溶液。

[0251] 本文公开的化合物的“代谢物”是当该化合物代谢时所形成的该化合物的衍生物。术语“活性代谢物”是指当化合物代谢时所形成的该化合物的生物活性衍生物。如本文所用的术语“代谢”是指生物体借此改变特定物质的过程的总和（包括但不限于水解反应和由酶催化的反应）。因此，酶使得化合物产生特定结构改变。例如，细胞色素P450催化多种氧化和还原反应，而二磷酸尿苷葡萄糖醛酸基转移酶催化激活的葡萄糖醛酸分子向芳族醇、脂族醇、羧酸、胺和游离巯基的转移。关于代谢的进一步信息可获自The Pharmacological Basis of Therapeutics，第9版，McGraw-Hill(1996)。本文公开的化合物的代谢物通过向宿主施用化合物并分析取自该宿主的组织样品，或者通过在体外将化合物与肝细胞一起温育并分析所得的化合物来鉴定。

[0252] “生物利用度”是指被递送至所研究的动物或人的体循环的本文所公开的化合物的重量百分比。药物在静脉内给药时的总暴露（$AUC_{(0-\infty)}$）通常被定义为100％可生物利用的（F％）。“口服生物利用度”是指与静脉内注射相比，当口服药物组合物时，本文所公开的化合物被吸收至体循环中的程度。

[0253] “血浆浓度”是指本文所公开的化合物在受试者血液的血浆成分中的浓度。应当理解，由于与代谢相关的变化性和/或与其他治疗剂的可能的相互作用，本文所述化合物的血浆浓度在受试者之间显著变化。根据本文公开的一个实施方案，本文公开的化合物的血浆浓度随受试者不同而不同。同样，诸如最大血浆浓度（C_{max}）或达到最大血浆浓度的时间（T_{max}）或血浆浓度时间曲线下总面积（$AUC_{(0-\infty)}$）等值也随受试者不同而不同。由于这种变化性，构成化合物的“治疗有效量”所需的量也随受试者不同而不同。

[0254] “药代动力学”是指决定在作用部位达到和保持适当药物浓度的因素。

药物组合物和给药方法的实例

[0255] 适当的给药途径包括但不限于：口服、静脉内、直肠、气雾剂、肠胃外、眼、肺、跨黏膜、经皮、阴道、耳、鼻、肌肉内注射、皮下注射和局部给药。另外，仅举例而言，肠胃外递送包括肌肉内、皮下、静脉内、髓内注射，以及鞘内、直接心室内、腹膜内、淋巴管内和鼻内注射。

[0256] 本文所述的药物制剂包括但不限于水性液体分散体、自乳化分散体、固溶体、脂质体分散体、气雾剂、固体剂型、粉末、立即释放制剂、控制释放制剂、速熔制剂、片剂、胶囊、丸剂、延迟释放制剂、延长释放制剂、脉冲式释放制剂、多颗粒制剂和混合的立即释放和控制释放制剂。

[0257] 在某些实施方案中，本文所述的化合物以局部方式而不是全身方式施用。在其他

实施方案中，本文所述的化合物以快速释放制剂的形式、以延长释放制剂的形式或以立即释放制剂的形式提供。在另外其他的实施方案中，本文所述的化合物是局部施用的。

[0258] 在一些实施方案中，将本文所述的化合物配制成药物组合物。在具体的实施方案中，药物组合物使用一种或多种生理学上可接受的载体以常规方式来配制，该载体包括赋形剂和辅料，其有利于将活性化合物加工为可药用的制品。合适的制剂取决于选择的给药途径。任何药学上可接受的技术、载体和赋形剂适当地用于配制本文所述的药物组合物：Remington：The Science and Practice of Pharmacy，第十九版（Easton，Pa.：Mack Publishing Company，1995）；Hoover，John E.，Remington's Pharmaceutical Sciences，Mack Publishing Co.，Easton，Pennsylvania 1975；Liberman，H.A. 和 Lachman，L，Eds.，Pharmaceutical Dosage Forms，Marcel Decker，New York，N.Y.，1980；以及 Pharmaceutical Dosage Forms and Drug Delivery Systems，第七版（Lippincott Williams&Wilkins 1999）。

[0259] 药物组合物是指本文所述的 HDAC8 抑制剂化合物与其他化学成分如载体、稳定剂、稀释剂、分散剂、悬浮剂、增稠剂和 / 或赋形剂的混合物。在某些实施方案中，药物组合物有助于对哺乳动物施用化合物。

[0260] 在一个实施方案中，本文所述的 HDAC8 抑制剂化合物在水溶液中配制。在具体的实施方案中，仅举例而言，该水溶液选自生理学上相容的缓冲液，如 Hank 溶液、Ringer 溶液或生理盐水缓冲液。在其他实施方案中，本文所述的 HDAC8 抑制剂化合物配制成用于跨黏膜给药。在具体的实施方案中，跨黏膜制剂包括适合于所要透过的屏障的渗透剂。在其中本文所述的化合物被配制成用于其他肠胃外注射的其他实施方案中，合适的制剂包括水溶液或非水溶液。

[0261] 在另一个实施方案中，本文所述的化合物被配制成用于口服给药。本文所述的化合物被配制成口服剂型，仅举例而言，该口服剂型包括片剂、粉末、丸剂、糖锭剂、胶囊、液体、凝胶、糖浆剂、酏剂、膏剂、悬浮液等。

[0262] 在某些实施方案中，用于口服使用的药物制剂如下获得：将一种或多种固体赋形剂与一种或多种本文所述的化合物混合，任选地研磨所得的混合物，并且如果需要在加入合适的辅料后将颗粒混合物加工以获得片剂或丸剂。合适的赋形剂特别是：填充剂，如糖类，包括乳糖、蔗糖、甘露醇或山梨醇；纤维素制剂，诸如：例如玉米淀粉、小麦淀粉、稻米淀粉、马铃薯淀粉、明胶、黄蓍胶、甲基纤维素、微晶纤维素、羟丙基甲基纤维素、羧甲基纤维素钠；或其他赋形剂，诸如：聚乙烯吡咯烷酮（PVP 或聚维酮）或磷酸钙。在具体的实施方案中，任选地添加崩解剂。仅举例而言，崩解剂包括交联羟甲基纤维素钠、聚乙烯吡咯烷酮、琼脂或海藻酸或其盐如海藻酸钠。

[0263] 口服剂型还包括由明胶制成的推入 - 配合式胶囊以及由明胶和诸如甘油或山梨醇的增塑剂制成的密封软胶囊。在具体的实施方案中，推入 - 配合式胶囊含有与一种或多种填充剂混合的活性成分。仅举例而言，填充剂包括：乳糖，诸如淀粉的粘合剂，和 / 或诸如滑石或硬脂酸镁的润滑剂，以及任选的稳定剂。在其他实施方案中，软胶囊含有溶解或悬浮在合适的液体中的一种或多种活性化合物。仅举例而言，合适的液体包括：一种或多种脂肪油、液体石蜡或液体聚乙二醇。另外，任选地添加稳定剂。

[0264] 在另外其他的实施方案中，局部施用本文所述的 HDAC8 抑制剂化合物。可局部施

用的组合物包括溶液、悬浮液、洗液、凝胶、糊剂、药棒、香膏、乳膏或软膏。

[0265] 在其他实施方案中，本文所述的 HDAC8 抑制剂化合物被配制成经吸入给药。适合于吸入给药的各种形式包括但不限于气雾剂、雾剂或粉末。

[0266] 药物组合物中的活性成分是游离酸或游离碱的形式或药学上可接受的盐的形式。另外，本文所述的方法和药物组合物包括使用 N- 氧化物、结晶形式（也称作多晶型物）以及这些化合物的具有相同类型活性的活性代谢物。本文所述的化合物的全部互变异构体都包括在本文提出的化合物的范围内。此外，本文所述的化合物包括非溶剂化形式以及用药学上可接受的溶剂如水、乙醇等溶剂化的形式。本文提出的化合物的溶剂化形式也被认为在本文中公开。另外，药物组合物任选地包含其他药物或制药剂、载体、佐剂，如防腐剂、稳定剂、润湿剂或乳化剂，溶液促进剂，用于调节渗透压的盐，缓冲液，和 / 或其他在治疗上有价值的物质。

[0267] 在某些实施方案中，含有本文所述化合物的组合物为了预防性和 / 或治疗性处置而施用。在某些治疗性应用中，以足以治愈或至少部分阻止疾病或状况的症状的量，向已患有该疾病或状况的患者施用该组合物。有效用于该用途的量取决于疾病或状况的严重程度和进程、以前的治疗、患者的健康状态、体重和对药物的反应，以及主治医师的判断。治疗有效量任选地通过包括但不限于剂量递增临床试验的方法来确定。

[0268] 在预防性应用中，向易患特定疾病、病症或状况或以其他方式具有其风险的患者施用含有本文所述化合物的组合物。在该用途中，精确量也取决于患者的健康状态、体重等。

[0269] 在一些实施方案中，药物组合物使用一种或多种生理学上可接受的载体以常规方式来配制，该载体包括赋形剂和辅料，其有利于将活性化合物加工为可药用的制品。合适的制剂取决于选择的给药途径。

给药方法和治疗方案的实例

[0270] 本文所述化合物用于制备用于抑制 HDAC8 或用于治疗至少部分地受益于 HDAC8 抑制的疾病或状况的药物。另外，用于治疗需要此类治疗的受试者的本文所述任何疾病或状况的方法包括向所述受试者施用治疗有效量的药物组合物，该药物组合物包含至少一种本文所述的化合物，或其药学上可接受的盐、药学上可接受的 N- 氧化物、药学活性代谢物、药学上可接受的前药或药学上可接受的溶剂化物。

[0271] 含有本文所述化合物的组合物为了预防性和 / 或治疗性处置而施用。在治疗性应用中，以足以治愈或至少部分阻止疾病或状况的症状的量，向已患有该疾病或状况的患者施用该组合物。有效用于该用途的量将取决于疾病或状况的严重程度和病程、先前的治疗、患者的健康状态、体重和对药物的反应，以及主治医师的判断。通过例如剂量递增临床试验来确定这样的治疗有效量。

[0272] 在预防性应用中，向易患特定疾病、病症或状况或以其他方式具有其风险的患者施用含有本文所述化合物的组合物。这样的量被定义为“预防有效量或剂量”。在这种用途中，精确量也取决于患者的健康状态、体重等。通过例如剂量递增临床试验来确定这样的预防有效量。当在患者中使用时，用于此用途的有效量将取决于疾病、病症或状况的严重程度和病程、先前的治疗、患者的健康状态和对药物的反应，以及主治医师的判断。

[0273] 在其中患者的状况没有改善的情况下，为了改善或者以其他方式控制或限制患者

的疾病或状况的症状，根据医生的裁量，化合物的施用长期地进行，即，持续延长的一段时间，包括患者的整个生命存续时间。

[0274] 在其中患者的状态没有改善的情况下，根据医生的裁量，化合物的施用连续地进行；或者，所施用的药物剂量在一段时间（即，“休药期”）内临时减少或临时暂停。休药期的长度为 2 天到 1 年不等，仅举例来说，包括 2 天、3 天、4 天、5 天、6 天、7 天、10 天、12 天、15 天、20 天、28 天、35 天、50 天、70 天、100 天、120 天、150 天、180 天、200 天、250 天、280 天、300 天、320 天、350 天或 365 天。在一些实施方案中，休药期内的剂量减少是从约 10％到约 100％，仅举例而言，包括约 10％、约 15％、约 20％、约 25％、约 30％、约 35％、约 40％、约 45％、约 50％、约 55％、约 60％、约 65％、约 70％、约 75％、约 80％、约 85％、约 90％、约 95％或约 100％。

[0275] 一旦患者状况发生改善，如果必要的话，施用维持剂量。随后，剂量或给药频率或二者根据症状的变化减少到疾病、病症或状况的改善得以保持的水平。当症状有任何复发时，一些患者需要长期的间歇性治疗。

[0276] 对应于此量的给定药剂的量将根据诸如特定化合物、疾病或状况及其严重程度、需要治疗的受试者或宿主的特性（例如体重）等因素而不同，不过将根据该病例的具体情况进行确定，所述情况包括例如施用的具体药剂、给药途径、所治疗的状况、所治疗的受试者或宿主。但是，一般而言，对成人治疗使用的剂量一般在每天约 0.02mg 至约 5000mg 的范围内，在其他实施方案中，在每天约 1mg 至约 1500mg 的范围内。在一些实施方案中，所需剂量在单一剂量中或作为分开的剂量呈现，所述分开的剂量同时（或在短时间内）或以适当的间隔施用，例如每天两次、三次、四次或更多次亚剂量。

[0277] 本文所述的药物组合物处于适合单次施用精确剂量的单位剂型中。在单位剂型中，制剂被分成含有适量的一种或多种化合物的单位剂量。该单位剂量是含有离散量的制剂的包装的形式。非限制性实例是包装的片剂或胶囊，和小瓶或安瓿中的粉末。水性悬浮组合物被包装在不可再次盖紧的单剂量容器中。或者，使用可再次盖紧的多剂量容器，在该情况下，组合物中一般包含防腐剂。仅举例来说，用于肠胃外注射的制剂呈现于包括但不限于安瓿的单位剂型中，或添加了防腐剂的多剂量容器中。

[0278] 适合于本文所述化合物的日剂量是从约 0.01mg/kg 至约 2.5mg/kg 体重。在包括但不限于人类的大型哺乳动物中，指示的日剂量在从约 0.5mg 至约 100mg 的范围内，以分开的剂量方便地施用，包括但不限于每天最多四次，或以延长释放的形式施用。用于口服给药的合适的单位剂型含有约 1mg 至约 50mg 的活性成分。前述范围仅是建议性的，因为关于个体治疗方案的变量数目很大，并且距离这些推荐值的相当大的偏离也并非不常见的。这样的剂量根据许多变量而改变，这些变量不限于所使用的化合物的活性、所治疗的疾病或状况、给药模式、受试个体的需求、所治疗的疾病或状况的严重程度，以及从业医生的判断。

[0279] 此类治疗方案的毒性和治疗效果通过标准药学程序在细胞培养物或实验动物中进行确定，包括但不限于 LD50（群体的 50％致死剂量）和 ED50（群体的 50％治疗有效剂量）的确定。毒性与治疗效果之间的剂量比是治疗指数，并且它表示成 LD50 与 ED50 之间的比值。显示出高治疗指数的化合物是此处所预期的。从细胞培养试验和动物研究获得的数据用于制定在人体中使用的剂量范围。在一些实施方案中，此类化合物的剂量处于包括 ED50 且具有最小毒性的循环浓度的范围内。剂量在该范围内变化，这取决于所使用的剂型

和所使用的给药途径。

联合治疗

[0280] 本文所述的化合物和组合物还与根据其对所治疗的状况的治疗价值而选择的其他治疗剂联合使用。通常，本文所述的组合物以及（在使用联合治疗的实施方案中）其他药剂不在同一药物组合物中施用，并且由于不同的物理和化学特性而通过不同的途径给药。根据确立的方案以及基于观察到的效果、剂量、给药模式和给药时间进行初始给药。

[0281] 在某些实例中，联合施用本文所述的至少一种化合物和其他治疗剂是合适的。仅举例而言，如果患者在接受一种本文的化合物如本文所述的异羟肟酸化合物时经受的副作用之一是恶心，那么联合施用抗恶心药剂和初始治疗剂是合适的。或者，仅举例而言，一种本文所述化合物的治疗效果通过佐剂的施用而增强（即，佐剂自身具有最小的治疗益处，但是与其他治疗剂联合时，会提高对患者的整体治疗益处）。或者，仅举例而言，患者经受的益处会通过联合施用一种本文所述化合物和也具有治疗益处的另一种治疗剂（其也包括治疗方案）而得到增强。在任何情况下，不管所治疗的疾病、病症或状况如何，患者经受的整体益处是两种治疗剂的累加或患者经受了协同益处。

[0282] 使用的化合物的具体选择将取决于主治医师的诊断和他们对患者的状况和适当的治疗方案的判断。化合物同时（例如同时、基本同时或在同一治疗方案内）或相继施用，这取决于疾病、病症或状况的性质，患者的状况，和使用的化合物的实际选择。治疗方案期间施用次序和各治疗剂的重复施用次数的确定是在对所治疗的疾病和患者状况的评估后确定的。

[0283] 对于本文所述的联合治疗，共同施用的化合物的剂量将根据使用的联合药物的类型、使用的具体药物、所治疗的疾病或状况等等而不同。另外，当与一种或多种生物活性剂共同施用时，本文提供的化合物与该生物活性剂或者同时施用或者相继施用。如果相继施用，主治医师将决定与生物活性剂联合施用蛋白质的适当顺序。

[0284] 无论如何，多种治疗剂（其中一种是本文所述的 HDAC8 选择性化合物）以任意次序施用或甚至同时施用。如果同时施用，多种治疗剂以单一的一体形式提供，或者以多种形式提供（仅举例而言，或者作为单一丸剂或者作为两种分开的丸剂）。在一些实施方案中，治疗剂以多个剂量给予，或者两种都作为多个剂量给予。如果不是同时施用，多个剂量间的时间从多于零周到少于四周不等。另外，组合方法、组合物和制剂并不限于仅两种药剂的使用；还设想了多重治疗组合的使用。

[0285] 可以理解，治疗、预防或改善寻求缓解的状况的剂量方案根据多种因素加以修改。这些因素包括受试者患有的病症或状况，以及受试者的年龄、体重、性别、饮食和医疗状况。因此，实际使用的剂量方案有很大不同，并因此可以偏离本文阐述的剂量方案。

[0286] 构成本文公开的联合治疗的药剂是联合剂型，或者是打算基本同时施用的单独剂型。构成联合治疗的药剂相继施用，其中任一治疗化合物通过要求两步施用的方案施用。该两步施用方案要求活性剂的相继施用，或者单独的活性剂的间隔施用。多个施用步骤之间的时间段从数分钟到数小时不等，这取决于各药剂的性质，例如药剂的效力、溶解度、生物利用度、血浆半衰期和动力学谱。靶分子浓度的生理节奏变化也决定最佳剂量间隔。

[0287] 另外，本文所述的化合物与向患者提供额外或协同益处的程序联合使用。仅举例而言，预期患者在本文所述的方法中将获得治疗和 / 或预防益处，其中本文公开的化合物

的药物组合物和/或与其他治疗剂的组合与遗传检测相结合，以确定个体是否是已知与某些疾病或状况相关的突变基因的携带者。

[0288] 本文所述的化合物和联合治疗在疾病或状况发生之前、期间或之后施用，并且包含化合物的组合物的施用时间有所不同。因此，例如，化合物用作预防剂，并且对具有发展为状况或疾病的倾向的受试者连续施用，以便预防该疾病或状况的发生。该化合物和组合物在症状发作期间或在症状发作后尽可能快地对受试者施用。化合物的施用在症状发作的最初48小时内开始，在其他实施方案中，在症状发作的最初48小时内开始，在另一实施方案中，在症状发作的最初6小时内开始，在又一实施方案中，在症状发作的3小时内开始。初始施用通过任何实用的途径进行，例如静脉内注射、浓注、5分钟到约5小时内的输注、丸剂、胶囊、透皮贴剂、颊部递送等，或其组合。在一些实施方案中，在检测到或怀疑疾病或状况发作后，在切实可行的情况下尽可能快地施用化合物，并且持续治疗该疾病所需的一段时间，例如约1个月到约3个月。对于各个受试者，治疗时长有所不同，并且使用已知的标准来确定该时长。例如，化合物或包含该化合物的制剂施用至少2周，在一些实施方案中，约1个月到约5年，在其他实施方案中，约1个月到约3年。

抗癌剂

[0289] 此处描述了本文所述的选择性HDAC8抑制剂与其他抗癌剂或化学治疗剂的组合。此类抗癌剂或化学治疗剂的实例可见于V.T.Devita和S.Hellman(编者)的Cancer Principles and Practice of Oncology，第六版(2001年2月15日)，Lippincott Williams&Wilkins Publishers。基于药物和有关的癌症的具体特性来确定药剂的组合。

[0290] 如本文所用的术语“组合”意指通过混合或组合超过一种活性成分而得到的产品，并且包括活性成分的固定和非固定组合。在一些实施方案中，该组合是固定组合。术语“固定组合”意指活性成分例如本文所述的肉桂酸羟基酰胺化合物和联合药剂两者以单一实体或剂量的形式同时向患者施用。在一些实施方案中，该组合是非固定组合。术语“非固定组合”意指活性成分例如本文所述的化合物和联合药剂作为单独的实体同时、并行或相继地向患者施用，没有具体的间隔时间限制，其中这样的施用在患者体内提供这两种化合物的有效水平。后者还适用于鸡尾酒疗法，例如三种或更多种活性成分的施用。

[0291] 在一个方面，本文公开的HDAC抑制剂与选自蒽环霉素(anthrocyclins)、氟达拉滨、夫拉平度、伊马替尼、硼替佐米、抗血管生成剂以及诸如全反式视黄酸和肿瘤坏死因子相关凋亡诱导配体等核受体配体联合施用。

[0292] 抗癌剂和/或在化学疗法中使用的药剂包括但不限于下列药剂：雌激素受体调节剂、雄激素受体调节剂、类视黄醇受体调节剂、细胞毒性/细胞抑制剂、抗增殖剂、异戊二烯基-蛋白质转移酶抑制剂、氮芥、亚硝基脲类、血管生成抑制剂、细胞增殖和存活信号途径抑制剂、细胞凋亡诱导剂、干扰细胞周期检查点的药剂、干扰受体酪氨酸激酶(RTK)的药剂、整联蛋白阻断剂、NSAID、固有的多药抗药性(MDR)的抑制剂、止吐剂、可用于治疗贫血的抑制剂、可用于治疗中性粒细胞减少的药剂、免疫增强药物、二膦酸盐类、芳香酶抑制剂、诱导肿瘤细胞的终末分化的药剂、γ-分泌酶抑制剂、癌症疫苗及它们的任意组合。

[0293] 在受试者患有癌症(例如，T细胞淋巴瘤)的情况下，选择性HDAC8抑制剂与一种或多种其他抗癌剂任意联合使用。抗癌剂的实例包括但不限于任何下列药剂：5-氮杂-2'-脱氧胞苷、全反式视黄酸、多柔比星、长春新碱、依托泊苷、吉西他滨、伊马替尼、

17-N- 烯丙基氨基 -17- 去甲氧基格尔德霉素 (17-AAG)、夫拉平度、LY294002、硼替佐米、曲妥珠单抗、BAY11-7082、PKC412 或 PD184352。

[0294] Taxol™ 亦被称为“紫杉醇”，是众所周知的抗癌药物，它通过增强和稳定微管形成而起作用，以及 Taxol™ 的类似物，如 Taxotere™。具有基本紫杉烷骨架作为共同结构特征的化合物也已表明由于稳定化微管而具有将细胞阻滞在 G2-M 期的能力，并且可用于与本文所述化合物联合治疗癌症。

[0295] 与选择性 HDAC8 抑制剂联合使用的其他抗癌剂包括阿霉素、放线菌素 D、博来霉素、长春碱、顺铂、阿西维辛；阿柔比星；盐酸阿考达唑；阿克罗宁；阿多来新；阿地白介素；六甲蜜胺；安波霉素；醋酸阿美蒽醌；氨鲁米特；安吖啶；阿那曲唑；安曲霉素；天冬酰胺酶；曲林菌素；阿扎胞苷；阿扎替派；阿佐霉素；巴马司他；苯佐替派；比卡鲁胺；盐酸比生群；二甲磺酸双奈法德；比折来新；硫酸博来霉素；布喹那钠；澳匹立明；白消安；放线菌素 C；卡芦睾酮；卡醋胺；卡贝替姆；卡铂；卡莫司汀；盐酸卡柔比星；卡折来新；西地芬戈；苯丁酸氮芥；西罗霉素；克拉屈滨；甲磺酸克立那托；环磷酰胺；阿糖胞苷；达卡巴嗪；盐酸柔红霉素；地西他滨；右奥马铂；地扎胍宁；甲磺酸地扎胍宁；地吖醌；盐酸多柔比星；屈洛昔芬；柠檬酸屈洛昔芬；丙酸屈他雄酮；达佐霉素；依达曲沙；盐酸依氟鸟氨酸；依沙芦星；恩洛铂；恩普氨酯；依匹哌啶；盐酸表柔比星；厄布洛唑；盐酸依索比星；雌莫司汀；雌莫司汀磷酸钠；依他硝唑；磷酸依托泊苷；氯苯乙嘧胺；盐酸法倔唑；法扎拉滨；芬维 A 胺；氟尿苷；磷酸氟达拉滨；氟尿嘧啶；氟西他滨；磷喹酮；福司曲星钠；盐酸吉西他滨；羟基脲；盐酸伊达比星；异环磷酰胺；伊莫福新 (iimofosine)；白介素 II(包括重组白介素 II 或 rIL2)、干扰素 α-2a；干扰素 α-2b；干扰素 α-n1；干扰素 α-n3；干扰素 β-1a；干扰素 γ-1b；异丙铂；盐酸依立替康；醋酸兰瑞肽；来曲唑；醋酸亮丙瑞林；盐酸利阿唑；洛美曲索钠；洛莫司汀；盐酸洛索蒽醌；马索罗酚；美登素；盐酸氮芥；醋酸甲地孕酮；醋酸美仑孕酮；美法仑；美诺立尔；巯基嘌呤；氨甲蝶呤；氨甲蝶呤钠；氯苯氨啶；美妥替哌；米丁度胺；米托克星；丝裂红素；米托洁林；米托马星；丝裂霉素；丝裂帕菌素；米托坦；盐酸米托蒽醌；麦考酚酸；诺考达唑；诺拉霉素；奥马铂；奥昔舒仑；培门冬酶；培利霉素；戊氮芥；硫酸培洛霉素；培磷酰胺；哌泊溴烷；哌泊舒凡；盐酸吡罗蒽醌；普卡霉素；普洛美坦；卟吩姆钠；泊非霉素；泼尼莫司汀；盐酸丙卡巴肼；嘌罗霉素；盐酸嘌罗霉素；吡唑呋喃菌素；利波腺苷；罗谷亚胺；沙芬戈；盐酸沙芬戈；司莫司汀；辛曲秦；磷乙酰天冬氨酸钠；司帕霉素；盐酸锗螺胺；螺莫司汀；螺铂；链黑菌素；链佐星；磺氯苯脲；他利霉素；替可加兰钠；替加氟；盐酸替洛蒽醌；替莫泊芬；替尼泊苷；替罗昔隆；睾内酯；硫咪嘌呤；硫鸟嘌呤；塞替派；噻唑呋林；替拉扎明；柠檬酸托瑞米芬；醋酸曲托龙；磷酸曲西立滨；三甲曲沙；三甲曲沙葡糖醛酸盐；曲普瑞林；盐酸妥布氯唑；乌拉莫司汀；乌瑞替派；伐普肽；维替泊芬；硫酸长春碱；长春地辛；硫酸长春地辛；硫酸长春匹定；硫酸长春甘酯；硫酸长春罗新；酒石酸长春瑞滨；硫酸长春罗定；硫酸长春利定；伏氯唑；折尼铂；净司他丁；盐酸佐柔比星。

[0296] 与选择性 HDAC8 抑制剂联合使用的其他抗癌剂包括：20- 表 -1,25- 二羟基维生素 D3；5- 乙炔基尿嘧啶；阿比特龙；阿柔比星；酰基富烯；腺环戊醇；阿多来新；阿地白介素；ALL-TK 拮抗剂；六甲蜜胺；氨莫司汀；2,4 二氯苯氧乙酸；氨磷汀；氨基酮戊酸；氨柔比星；安吖啶；阿那格雷；阿那曲唑；穿心莲内酯；血管生成抑制剂；拮抗剂 D；拮抗剂 G；安雷利克斯；抗背部化形态发生蛋白 -1；抗雄激素，前列腺癌；抗雌激素；抗瘤酮；反义寡核

苷酸；甘氨酸阿非科林；凋亡基因调节剂；凋亡调节剂；脱嘌呤核酸；ara-CDP-DL-PTBA；精氨酸脱氨酶；9-[2- 甲氧基 -4-(甲基磺酰基氨基) 苯基氨基]-N,5- 二甲基 -4- 吖啶甲酰胺 (asulacrine)；阿他美坦；阿莫司汀；axinastatin1；axinastatin2；axinastatin3；阿扎司琼；阿扎毒素；重氮酪氨酸；浆果赤霉素 III 衍生物；巴兰醇 (balanol)；巴马司他；BCR/ABL 拮抗剂；苯并绿素类；苯甲酰基星孢菌素；β 内酰胺衍生物；β-alethine；贝塔克拉霉素 (betaclamycin)B；白桦脂酸；bFGF 抑制剂；比卡鲁胺；比生群；二吖丙啶基精胺；双奈法德；二枸橼酸环己噻草酯 A；比折来新；布福雷 (breflate)；澳匹立明；布度钛；丁硫氨酸亚砜胺；卡泊三醇；钙感光蛋白 C(calphostin C)；喜树碱衍生物；金丝雀痘 IL-2；卡培他滨；甲酰胺 - 氨基 - 三唑；羧基酰胺基三唑；CaRest M3；CARN 700；软骨源的抑制剂；卡折来新；酪蛋白激酶抑制剂 (ICOS)；栗精胺；天蚕抗菌肽 B；西曲瑞克；二氢卟酚 (chlorlns)；磺胺氯喹喔啉；西卡前列素；顺式卟啉；克拉屈滨；氯米芬类似物；克霉唑；考利丝霉素 (collismycin)A；考利丝霉素 B；考布他汀 A4；考布他汀类似物；conagenin；crambescidin 816；克立那托；念珠藻素 8；念珠藻素 A 衍生物；curacin A；环戊蒽醌；环铂 (cycloplatam)；赛可霉素 (cypemycin)；阿糖胞苷十八烷基磷酸钠；细胞裂解因子；磷酸己烷雌酚；达昔单抗；地西他滨；脱氢膜海鞘素 (dehydrodidemnin)B；地洛瑞林；地塞米松；右异环磷酰胺；右雷佐生；右维拉帕米；地吖醌；膜海鞘素 B；3,4- 二羟基苯并氧肟酸 (didox)；二乙基去甲精胺；二氢 -5- 氮杂胞苷；9- 二草霉素；二苯基螺莫司汀；二十二烷醇；多拉司琼；去氧氟尿苷；屈洛昔芬；屈大麻酚；多卡霉素 (duocarmycin)SA；依布硒；依考莫司汀；依地福新；依决洛单抗；依氟鸟氨酸；榄香烯；乙嘧替氟；表柔比星；爱普列特；雌莫司汀类似物；雌激素激动剂；雌激素拮抗剂；依他硝唑；磷酸依托泊苷；依西美坦；法倔唑；法扎拉滨；芬维 A 胺；非格司亭；非那雄胺；氟卓斯汀；荧蒽固酮；氟达拉滨；盐酸氟道诺霉素；福酚美克；福美坦；福司曲星；福莫司汀；得克萨菲啉钆；硝酸镓；加洛他滨；加尼瑞克；明胶酶抑制剂；吉西他滨；谷胱甘肽抑制剂；氨基磺酸 1,7- 庚烷二基酯 (hepsulfam)；神经生长因子 (heregulin)；六亚甲基二乙酰胺；金丝桃素；伊班膦酸；伊达比星；艾多昔芬；伊决孟酮；伊莫福新；伊洛马司他；咪唑并吖啶酮；咪喹莫特；免疫刺激肽；胰岛素如生长因子 -1 受体抑制剂；干扰素激动剂；干扰素；白介素；碘苄胍；碘阿霉素；4- 甘薯醇；伊罗普拉；伊索拉定；异邦格唑 (isobengazole)；isohomohalicondrin B；伊他司琼；jasplakinolide；kahalalide F；三乙酸片螺素 -N；兰瑞肽；雷那霉素 (leinamycin)；来格司亭；硫酸香菇多糖；leptolstatin；来曲唑；白血病抑制因子；白细胞 α 干扰素；亮丙瑞林 + 雌激素 + 孕酮；亮丙瑞林；左旋咪唑；利阿唑；线形聚胺类似物；亲脂性二糖肽；亲脂性铂化合物；lissoclinamide 7；洛铂；蚯蚓磷脂；洛美曲索；氯尼达明；洛索蒽醌；洛伐他汀；洛索立宾；勒托替康；得克萨菲啉镥；1-((R)-5- 羟基己基) 可可碱 (lysofylline)；裂解肽；美坦新；mannostatin A；马立马司他；马索罗酚；乳腺丝氨酸蛋白酶抑制蛋白 (maspin)；基质溶解素抑制剂；基质金属蛋白酶抑制剂；美诺立尔；美巴龙；美替瑞林；甲硫氨酸酶；甲氧氯普胺；MIF 抑制剂；米非司酮；米替福新；米立司亭；错配的双链 RNA；米托胍腙；二澳卫矛醇；丝裂霉素类似物；米托萘胺；迈托毒素 (mitotoxin) 成纤维细胞生长因子 - 皂草素；米托蒽醌；莫法罗汀；莫拉司亭；单克隆抗体，人绒毛膜促性腺激素；单磷酰基脂质 A+ 分支杆菌细胞壁 sk；莫哌达醇；多药抗药性基因抑制剂；基于多肿瘤抑制剂 1 的治疗；芥抗癌剂；mycaperoxide B；分枝杆菌细胞壁提取物；myriaporone；

N- 乙酰基地那林 ;N- 取代苯甲酰胺 ;那法瑞林 ;nagrestip ;纳洛酮 + 镇痛新 ;napavin ;萘萜二醇 ;那托司亭 ;奈达铂 ;奈莫柔比星 ;奈立膦酸 ;中性肽链内切酶 ;尼鲁米特 ;尼沙霉素 (nisamycin) ;一氧化氮调节剂 ;硝基氧抗氧化剂 ;nitrullyn ;O6- 苄基鸟嘌呤 ;奥曲肽 ;okicenone ;寡核苷酸 ;奥那司酮 ;昂丹司琼 ;昂丹司琼 ;双氯非那胺 (oracin) ;口服细胞因子诱导剂 ;奥马铂 ;奥沙特隆 ;奥沙利铂 ;奥克萨霉素 (oxaunomycin) ;帕劳胺 ;棕榈酰根瘤菌素 ;帕米膦酸 ;人参三醇 ;帕诺米芬 ;六配位儿茶胺铁螯合剂副菌铁素 (parabactin) ;帕折普汀 ;培门冬酶 ;培得星 ;戊聚糖聚硫酸钠 ;喷司他丁 ;盘托唑 (pentrozole) ;全氟溴烷 ;培磷酰胺 ;紫苏子醇 ;吩嗪霉素 (phenazinomycin) ;乙酸苯酯 ;磷酸酶抑制剂 ;毕西巴尼 ;盐酸匹鲁卡品 ;吡柔比星 ;吡曲克辛 ;胎盘素 (placetin)A ;胎盘素 (placetin)B ;纤溶酶原激活剂的抑制剂 ;铂复合物 ;铂化合物 ;铂 - 三胺复合物 ;卟吩姆钠 ;泊非霉素 ;泼尼松 ;丙基二 - 吖啶酮 ;前列腺素 J2 ;蛋白酶体抑制剂 ;基于蛋白 A 的免疫调节剂 ;蛋白激酶 C 抑制剂 ;蛋白激酶 C 抑制剂,微藻 ;蛋白酪氨酸磷酸酶抑制剂 ;嘌呤核苷磷酸化酶抑制剂 ;羟基茜草素 ;吡唑啉吖啶 ;吡醇羟乙酯化血红蛋白聚氧乙烯共轭物 ;raf 拮抗剂 ;雷替曲塞 ;雷莫司琼 ;ras 法呢基蛋白转移酶抑制剂 ;ras 抑制剂 ;ras-GAP 抑制剂 ;去甲基瑞替普汀 ;依替膦酸铼 Re 186 ;根霉素 ;核酶 ;RII 维 A 胺 ;罗谷亚胺 ;罗希吐碱 ;罗莫肽 ;罗喹美克 ;rubiginone B1 ;ruboxyl ;沙芬戈 ;saintopin ;SarCNU ;肌植醇 (sarcophytol)A ;沙格司亭 ;Sdi 1 模拟物 ;司莫司汀 ;衰老来源抑制剂 1 ;有义寡核苷酸 ;信号转导抑制剂 ;信号转导调节剂 ;单链抗原结合蛋白 ;西佐喃 ;索布佐生 ;硼卡钠 ;苯乙酸钠 ;solverol ;生长调节素结合蛋白 ;索纳明 ;膦门冬酸 ;斯拜可霉素 (spicamycin)D ;螺莫司汀 ;脾脏五肽 ;CD- 螺环缩酮前体 δ - 内酯 1 ;鲨胺 ;干细胞抑制剂 ;干细胞分裂抑制剂 ;stipiamide ;基质溶解素抑制剂 ;sulfinosine ;强效的血管活性肠肽拮抗剂 ;suradista ;舒拉明 ;苦马豆碱 ;合成的糖胺聚糖 ;他莫司汀 ;他莫昔芬甲碘化物 ;牛磺莫司汀 ;他扎罗汀 ;替可加兰钠 ;替加氟 ;tellurapyrylium ;端粒酶抑制剂 ;替莫泊芬 ;替莫唑胺 ;替尼泊苷 ;十氧化四氯 ;四氮胺 (tetrazomine) ;唐松草碱 ;噻可拉林 ;血小板生成素 ;血小板生成素模拟物 ;胸腺法新 ;胸腺生成素受体激动剂 ;胸腺曲南 ;促甲状腺激素 ;乙基锡初紫红素 ;替拉扎明 ;二氯钛烯 ;topsentin ;托瑞米芬 ;全能干细胞因子 ;翻译抑制剂 ;维甲酸 ;三乙酰基尿苷 ;曲西立滨 ;三甲曲沙 ;曲普瑞林 ;托烷司琼 ;妥罗雄脲 ;酪氨酸激酶抑制剂 ;酪氨酸磷酸化抑制剂 (tyrphostins) ;UBC 抑制剂 ;乌苯美司 ;泌尿生殖窦源的生长抑制因子 ;尿激酶受体拮抗剂 ;伐普肽 ;variolin B ;载体系统,红细胞基因治疗 ;维拉雷琐 ;藜芦胺 ;verdins ;维替泊芬 ;长春瑞滨 ;长春磷汀 ;维他辛 (vitaxin) ;伏氯唑 ;扎诺特隆 ;折尼铂 ;亚苄维 C ;和净司他丁斯酯。

[0297] 与选择性 HDAC8 抑制剂联合使用的又一些其他的抗癌剂包括烷化剂、抗代谢物、天然产物或激素,氮芥类 (例如氮芥、环磷酰胺、苯丁酸氮芥等)、烷基磺酸酯 (例如白消安)、亚硝基脲 (例如卡莫司汀、洛莫司汀等) 或三氮烯类 (氨烯咪胺等)。抗代谢物的实例包括但不限于叶酸类似物 (例如氨甲蝶呤) 或嘧啶类似物 (例如阿糖胞苷)、嘌呤类似物 (例如巯基嘌呤、硫鸟嘌呤、喷司他丁)。

[0298] 可以与选择性 HDAC8 抑制剂联合使用的天然产物的实例包括但不限于长春花生物碱类 (例如长春碱、长春新碱)、表鬼臼毒素类 (例如依托泊苷)、抗生素类 (例如柔红霉素、多柔比星、博来霉素)、酶类 (例如 L- 天冬酰胺酶) 或生物应答调节剂 (例如干扰素

α)。

[0299] 与选择性 HDAC8 抑制剂联合使用的烷化剂的实例包括但不限于氮芥类(例如氮芥、环磷酰胺、苯丁酸氮芥、美法仑等)、乙烯亚胺和甲基三聚氰胺(例如六甲基三聚氰胺、塞替派)、烷基磺酸酯(例如白消安)、亚硝基脲(例如卡莫司汀、洛莫司汀、司莫司汀、链佐星等)或三氮烯类(氨烯咪胺等)。抗代谢物的实例包括但不限于叶酸类似物(例如氨甲蝶呤)或嘧啶类似物(例如氟尿嘧啶、氟尿苷、阿糖胞苷)、嘌呤类似物(例如巯基嘌呤、硫鸟嘌呤、喷司他丁)。

[0300] 可以与选择性 HDAC8 抑制剂联合使用的激素和拮抗剂的实例包括但不限于肾上腺皮质类固醇类(例如强的松)、孕激素类(例如己酸羟孕酮、醋酸甲地孕酮、醋酸甲羟孕酮)、雌激素类(例如二乙基己烯雌酚、乙炔雌二醇)、抗雌激素(例如他莫昔芬)、雄激素类(例如丙酸睾酮、氟甲睾酮)、抗雄激素(例如氟他胺)、促性腺素释放激素类似物(例如亮丙瑞林,SPD-424)。

[0301] 在另一个实施方案中,Dynepo 基因激活的促红细胞生成素(抗贫血药;人促红细胞生成素)与选择性 HDAC8 抑制剂化合物联合施用。

[0302] “雌激素受体调节剂”是指无论采用何种机理,能干扰或抑制雌激素与受体结合的化合物。雌激素受体调节剂的实例包括但不限于,他莫昔芬、雷洛昔芬、艾多昔芬、LY353381、LY117081、托瑞米芬、氟维司群、4-[7-(2,2- 二甲基 -1- 氧代丙氧基 -4- 甲基 -2-[4-[2-(1- 哌啶基)乙氧基]苯基]-2H-1- 苯并吡喃 -3- 基)- 苯基 -2,2- 二甲基丙酸酯、4,4’- 二羟基二苯甲酮 -2,4- 二硝基苯基 - 腙以及 SH646。在一些实施方案中,雌激素受体调节剂是他莫昔芬和雷洛昔芬。

[0303] “雄激素受体调节剂”是指无论采用何种机理,能干扰或抑制雄激素与受体结合的化合物。雄激素受体调节剂的实例包括非那雄胺和其他 5α- 还原酶抑制剂、尼鲁米特、氟他胺、比卡鲁胺、利阿唑以及醋酸阿比特龙。

[0304] “类视黄醇受体调节剂”是指无论采用何种机理,能干扰或抑制类视黄醇与受体结合的化合物。此类类视黄醇受体调节剂的实例包括贝沙罗汀、维甲酸、13- 顺 - 视黄酸、9- 顺 - 视黄酸、α- 二氟甲基鸟氨酸、ILX23-7553、反式 -N-(4’- 羟甲苯)维甲酰胺以及 N-4- 羧基苯基维甲酰胺。

[0305] 在用于治疗或预防癌症的本文所述的方法和组合物中使用的其他药剂包括铂配位复合物(例如顺铂、卡铂)、蒽醌(例如米托蒽醌)、取代脲(例如羟基脲)、甲基肼衍生物(例如丙卡巴肼)、肾上腺皮质抑制剂(例如米托坦、氨鲁米特)。

[0306] 通过由于稳定化微管来将细胞阻滞于 G2-M 期而起作用并且与选择性 HDAC8 抑制剂联合使用的抗癌剂实例包括但不限于下列市售药物和开发中的药物:厄布洛唑 (Erbulozole,也称为 R-55104)、多拉司他汀 10(Dolastatin 10,也称为 DLS-10 和 NSC-376128)、羟乙基磺酸米伏布林 (Mivobulin isethionate,也称为 CI-980)、长春新碱、NSC-639829、圆皮海绵内酯 (Discodermolide,也称为 NVP-XX-A-296)、ABT-751(Abbott,也称为 E-7010)、阿托瑞亭 (Altorhyrtin,诸如阿托瑞亭 A 和阿托瑞亭 C)、海绵抑素 (Spongistatin,诸如海绵抑素 1、海绵抑素 2、海绵抑素 3、海绵抑素 4、海绵抑素 5、海绵抑素 6、海绵抑素 7、海绵抑素 8 和海绵抑素 9)、盐酸西马多丁 (Cemadotin hydrochloride,也称为 LU-103793 和 NSC-D-669356)、埃博霉素类(诸如埃博霉素 A、埃博霉素 B、埃博霉

素 C(也称为脱氧埃博霉素 A 或 dEpoA)、埃博霉素 D(也称为 KOS-862、dEpoB 和脱氧埃博霉素 B)、埃博霉素 E、埃博霉素 F、埃博霉素 BN- 氧化物、埃博霉素 AN- 氧化物、16- 氮杂埃博霉素 B、21- 氨基埃博霉素 B(也称为 BMS-310705)、21- 羟基埃博霉素 D(也称为脱氧埃博霉素 F 和 dEpoF)、26- 氟埃博霉素)、阿瑞他丁 PE(Auristatin PE,也称为 NSC-654663)、索利多丁 (Soblidotin,也称为 TZT-1027)、LS-4559-P(Pharmacia,也称为 LS-4577)、LS-4578(Pharmacia,也称为 LS-477-P)、LS-4477(Pharmacia)、LS-4559(Pharmacia)、RPR-112378(Aventis)、硫酸长春新碱、DZ-3358(Daiichi)、FR-182877(Fujisawa,也称为 WS-9885B)、GS-164(Takeda)、GS-198(Takeda)、KAR-2(Hungarian Academy of Sciences)、BSF-223651(BASF,也称为 ILX-651 和 LU-223651)、SAH-49960(Lilly/Novartis)、SDZ-268970(Lilly/Novartis)、AM-97(Armad/Kyowa Hakko)、AM-132(Armad)、AM-138(Armad/Kyowa Hakko)、IDN-5005(Indena)、念珠藻素 52(Cryptophycin 52,也称为 LY-355703)、AC-7739(Ajinomoto,也称为 AVE-8063A 和 CS-39.HCI)、AC-7700(Ajinomoto,也称为 AVE-8062、AVE-8062A、CS-39-L-Ser.HCI 和 RPR-258062A)、Vitilevuamide、Tubulysin A、Canadensol、矢车菊黄素 (Centaureidin,也称为 NSC-106969)、T-138067(Tularik,也称为 T-67,TL-138067 和 TI-138067)、COBRA-1(Parker Hughes Institute,也称为 DDE-261 和 WHI-261)、H10(Kansas State University)、H16(Kansas State University)、奥可西丁 A1(Oncocidin A1,也称为 BTO-956 和 DIME)、DDE-313(Parker Hughes Institute)、Fijianolide B、Laulimalide、SPA-2(Parker Hughes Institute)、SPA-1(Parker Hughes Institute,也称为 SPIKET-P)、3-IAABU(细胞骨架 /Mt.Sinai School of Medicine,也称为 MF-569)、宁咳平 (Narcosine)(也称为 NSC-5366)、那可丁 (Nascapine)、D-24851(Asta Medica)、A-105972(Abbott)、哈米特林 (Hemiasterlin)、3-BAABU(细胞骨架 /Mt.Sinai School of Medicine,也称为 MF-191)、TMPN(Arizona State University)、双钒乙酰丙酮化物、T-138026(Tularik)、Monsatrol、lnanocine(也称为 NSC-698666)、3-lAABE(细胞骨架 /Mt.Sinai School of Medicine)、A-204197(Abbott)、T-607(Tuiarik,也称为 T-900607)、RPR-115781(Aventis)、艾榴素 (Eleutherobin,诸如去甲基艾榴素、去乙酰基艾榴素、异艾榴素 A 和 Z- 艾榴素)、Caribaeoside、Caribaeolin、软海绵素 B(HalichondrinB)、D-64131(Asta Medica)、D-68144(Asta Medica)、含氯环肽 A(Diazonamide A)、A-293620(Abbott)、NPI-2350(Nereus)、根薯酮内酯 A(Taccalonolide A、TUB-245(Aventis)、A-259754(Abbott)、Diozostatin、(-)-Phenylahistin(也称为 NSCL-96F037)、D-68838(Asta Medica)、D-68836(Asta Medica)、肌基质蛋白 B(Myoseverin B)、D-43411(Zentaris,也称为 D-81862)、A-289099(Abbott)、A-318315(Abbott)、HTI-286(也称为 SPA-110,三氟醋酸盐)(Wyeth)、D-82317(Zentaris)、D-82318(Zentaris)、SC-12983(NCI)、Resverastatin 磷酸钠、BPR-OY-007(National Health Research Institutes) 和 SSR-250411(Sanofi)。

[0307] “细胞毒性 / 细胞抑制剂”是指这样的化合物 :其主要通过直接干扰细胞的功能而引起细胞死亡或抑制细胞增殖,或抑制或干扰细胞有丝分裂,该化合物包括烷化剂、肿瘤坏死因子、嵌入剂、低氧可激活的化合物、微管抑制剂 / 微管稳定剂、有丝分裂驱动蛋白抑制剂、组蛋白脱乙酰酶抑制剂、参与有丝分裂进程的激酶的抑制剂、抗代谢物 ;生物应答调节剂 ;激素 / 抗激素治疗剂、造血生长因子、单克隆抗体靶向治疗剂、拓扑异构酶抑制剂、蛋白

酶体抑制剂和遍在蛋白连接酶抑制剂。

[0308] 细胞毒性剂的实例包括但不限于：替拉扎明 (tirapazimine)、sertenef、恶病质素、异环磷酰胺、他索纳明、氯尼达明、卡铂、六甲蜜胺、泼尼莫司汀、二澳卫矛醇、雷莫司汀、福莫司汀、奈达铂、奥沙利铂、替莫唑胺、庚铂 (heptaplatin)、雌莫司汀、甲苯磺酸英丙舒凡 (improsulfan tosilate)、曲磷胺、尼莫司汀、二澳螺氯铵、嘌嘧替派、洛铂、沙铂、甲基丝裂霉素、顺铂、伊罗夫文、右异环磷酰胺 (dexifosfamide)、顺 - 胺二氯 (2- 甲基 - 吡啶) 铂、苄基鸟嘌呤、葡磷酰胺、GPX100、(反式，反式，反式)- 双 -mu-(己烷 -1，6- 二胺)-mu-[二胺 - 铂 (II)] 双 [二胺 -(氯) 铂 (II)]- 四氯化物、二吖丙啶基精胺 (diarizidinylspermine)、三氧化二砷、1-(11- 十二烷基氨基 -10- 羟基十一烷基)-3，7- 二甲基黄嘌呤、佐柔比星、伊达比星、柔红霉素、比生群、米托蒽醌、吡柔比星、吡荼非特、戊柔比星、氨柔比星、抗瘤酮、3’- 脱氨基 -3’ 吗啉代 -13- 脱氧 -10- 羟基洋红霉素、安那霉素、加柔比星、依利奈法德、MEN10755 和 4- 脱甲氧基 -3- 脱氨基 -3- 吖丙啶基 -4- 甲基磺酰基柔红霉素 (见 WOOO/50032)。

[0309] 微管抑制剂的实例包括：紫杉醇、硫酸长春地辛、3’，4’- 二脱氢 -4’- 脱氧 -8’- 去甲长春碱、多西他赛、根霉素、多拉司他汀、羟乙基磺酸米伏布林、奥瑞他汀、西马多丁、RPR109881、BMS184476、长春氟宁、念珠藻素、2，3，4，5，6- 五氟 -N-(3- 氟 -4- 甲氧基苯基)- 苯磺酰胺、脱水长春碱、N，N- 二甲基 -L- 缬氨酰 -L- 缬氨酰 -N- 甲基 -L- 缬氨酰 -L- 脯氨酰 -L- 脯氨酸 - 叔丁基酰胺、TDX258 和 BMS188797。

[0310] 拓扑异构酶抑制剂的一些实例是托泊替康、hycaptamine、伊立替康、芦比替康、6- 乙氧基丙酰基 -3’，4’ -O- 外 - 苯亚甲基 - 教酒菌素、9- 甲氧基 -N，N- 二甲基 -5- 硝基吡唑并 [3，4，5-KL] 吖啶 -2-(6H) 丙胺、1- 氨基 -9- 乙基 -5- 氟 -2，3- 二羟基 -9- 羟基 -4- 甲基 -1H，12H- 苯并 [de] 吡喃酮 [3’，4’ :b，7]- 吲嗪并 [1，2b] 喹啉 -10，13(9H，15H) 二酮、勒托替康、7-[2-(N- 异丙基氨基)- 乙基]-(20S) 喜树碱、BNP1350、BNPI1100、BN80915、BN80942、磷酸依托泊苷、替尼泊苷、索布佐生、2’- 二甲基氨基 -2’- 脱氧 - 依托泊苷、GL331、N-[2-(二甲基氨基) 乙基]-9- 羟基 -5，6- 二甲基 -6H- 吡啶并 [4，3-B] 咔唑 -1- 甲酰胺、9-[2- 甲氧基 -4-(甲基磺酰基氨基) 苯基氨基]-N，5- 二甲基 -4- 吖啶甲酰胺 (asulacrine)、(5a，5aB，8aa，9b)-9-[2-[N-[2-(二甲基氨基) 乙基]-N- 甲基氨基] 乙基]-5-[4- 羟基 -3，5- 二甲氧基苯基]-5，5a，6，8，8a，9- 六氢呋喃并 (3’，4’ :6，7) colchic(2，3-d)-1，3- 二氧杂环戊烯 -6- 酮、2，3-(亚甲基二氧基)-5- 甲基 -7- 羟基 -8- 甲氧基苯并 [c]- 菲啶鎓、6，9- 双 [(2- 氨基乙基)- 氨基] 苯并 [g] 异喹啉 -5，10- 二酮、5-(3- 氨基丙氨基)-7，10- 二羟基 -2-(2- 羟基乙基氨基甲基)-6H- 吡唑并 [4，5，1-de] 吖啶 -6- 酮、N-[1-[2(二乙基氨基) 乙基氨基]-7- 甲氧基 -9- 氧代 -9H- 噻吨 -4- 基甲基] 甲酰胺、N-(2-(二甲基氨基) 乙基) 吖啶 -4- 甲酰胺、6-[[2-(二甲基氨基) 乙基] 氨基]-3- 羟基 -7H- 茚并 [2-，1-c] 喹啉 -7 酮和地美司钠。

[0311] “抗增殖剂”包括反义 RNA 和 DNA 寡核苷酸如 G3139、ODN698、RVASKRAS、GEM231 和 INX3001，以及抗代谢物如依诺他滨、卡莫氟、替加氟、喷司他丁、去氧氟尿苷、三甲曲沙、氟达拉滨、卡培他滨、加洛他滨、阿糖胞苷十八烷基磷酯、fosteabine 钠水合物、雷替曲塞、paltitrexid、乙嘧替氟、噻唑呋林、地西他滨、诺拉曲克、培美曲塞、奈拉滨、2’- 脱氧 -2’- 亚甲基胞苷、2’- 氟亚甲基 -2’- 脱氧胞苷、N-[5(2，3- 二氢 - 苯并呋喃基) 磺酰

基]-N'-(3,4-二氯苯基)脲、N6-[4-脱氧-4-[N2-[2(E),4(E)-十四碳二烯酰基]-甘氨酰基氨基]-L-甘油基-B-L-甘露-吡喃庚糖基]-腺嘌呤、阿普立定、海鞘素、曲沙他滨、4-[2-氨基-4-氧代-4,6,7,8-四氢-3H-嘧啶并[5,4-b][1,4]噻嗪-6-基-(S)-乙基]-2,5-噻吩酰基-L-谷氨酸、氨基蝶呤、5-氟尿嘧啶、阿拉诺新、11-乙酰基-8-(氨基甲酰基氧基甲基)-4-甲酰基-6-甲氧基-14-氧杂-1,11-二氮杂四环(7.4.1.0.0)-十四碳-2,4,6-三烯-9-基乙酸酯、苦马豆素、洛美曲索、右雷佐生、甲硫氨酸酶、2'-氰基-2'-脱氧-N4-棕榈酰基-1-B-D-阿拉伯呋喃糖基胞嘧啶和3-氨基吡啶-2-甲醛缩氨基硫脲。"抗增殖剂"还包括除"血管生成抑制剂"下所列的之外的生长因子单克隆抗体,如曲妥珠单抗,以及肿瘤抑制基因如p53,其通过重组病毒介导的基因转移进行递送(参见,例如,美国专利6,069,134)。

[0312] "异戊二烯基-蛋白转移酶抑制剂"是指抑制异戊二烯基-蛋白转移酶类中的任何一个或任何组合的化合物,该异戊二烯基-蛋白转移酶包括法呢基-蛋白转移酶(FPTase)、I型香叶基香叶基-蛋白转移酶(GGPTase-I)和II型香叶基香叶基-蛋白转移酶(GGPTase-II,亦称为Rab GGPTase)。异戊二烯基-蛋白转移酶抑制化合物的实例包括(±)-6-[氨基(4-氯苯基)(1-甲基-1H-咪唑-5-基)甲基]-4-(3-氯苯基)-1-甲基-2(1H)-喹啉酮、(-)-6-[氨基(4-氯苯基-1)(1-甲基-1H-咪唑-5-基)甲基]-4-(3-氯苯基)-1-甲基-2(1H)-喹啉酮、(+)-6-[氨基(4-氯苯基)(1-甲基-1H-咪唑-5-基)甲基]-4-(3-氯苯基)-1-甲基-2(1H)-喹啉酮、5(S)-n-丁基-1-(2,3-二甲基-苯基)-4-[1-(4-氰基苄基)-5-咪唑基甲基]-2-哌嗪酮、(S)-1-(3-氯苯基)-4-[1-(4-氰基苄基)-5-咪唑基甲基]-5-[2-(乙磺酰基)-甲基)-2-哌嗪酮、5(S)-n-丁基-1-(2-甲基苯基)-4-[1-(4-氰基苄基)-5-咪唑基甲基]-2-哌嗪酮、1-(3-氯苯基)-4-[1-(4-氰基苄基)-2-甲基-5-咪唑基甲基]-2-哌嗪酮、1-(2,2-二苯基乙基)-3-[N-(1-(4-氰基苄基)-1H-咪唑-5-基-乙基)氨基甲酰基]-哌啶、4-{5-[4-羟基甲基-4-(4-氯吡啶-2-基甲基)-哌啶-1-基甲基]-2-甲基咪唑-1-基甲基}苄腈、4-{5-[4-羟基甲基-4-(3-氯苄基)-哌啶-1-基甲基]-2-甲基咪唑-1-基甲基}苄腈、4-{3-[4-(2-氧代-2H-吡啶-1-基)苄基]-3H-咪唑-4-基甲基}苄腈、4-{3-[4-(5-氯-2-氧代-2H-[1,2']联吡啶-5'-基甲基]-3H-咪唑-4-基甲基}苄腈、4-{3-[4-(2-氧代-2H-[1,2']联吡啶-5'-基甲基]-3H-咪唑-4-基甲基}苄腈、4-[3-(2-氧代-1-苯基-1,2-二氢吡啶-4-基甲基)-3H-咪唑-4-基甲基}苄腈、18,19-二氢-19-氧代-5H,17H-6,10:12,16-二甲桥-1H-咪唑并[4,3-c][1,11,4]二氧杂-氮杂十九环-9-甲腈、(±)-19,20-二氢-19-氧代-5H-18,21-乙桥-12,14-乙烯桥-6,10-甲桥-22H-苯并[d]咪唑并[4,3-k][1,6,9,12]-氧杂三氮杂-十八环-9-甲腈、19,20-二氢-19-氧代-5H,17H-18,21-乙桥-6,10:12,16-二甲桥-22H-咪唑并[3,4-h][1,8,11,14]氧杂三氮杂二十环-9-甲腈和(±)-19,20-二氢-3-甲基-19-氧代-5H-18,21-乙桥-12,14-乙烯桥-6,10-甲桥-22H-苯并[d]咪唑并[4,3-k][1,6,9,12]氧杂-三氮杂十八环-9-甲腈。

[0313] 关于异戊二烯基-蛋白转移酶抑制剂对血管生成的作用的实例参见J.Of Cancer,Vol.35,No.9,pp.1394-1401(1999)。

[0314] HIV蛋白酶抑制剂的实例包括氨普那韦、阿巴卡韦、CGP-73547、CGP-61755、DMP-450、茚地那韦、奈非那韦、替拉那韦、利托那韦、沙奎那韦、ABT-378、AG1776和

BMS-232。逆转录酶抑制剂的实例包括地拉夫定、依法韦仑、GS-840、HB Y097、拉米夫定、奈韦拉平、齐多夫定、拉米夫定、ddC 和 dd1。已经报道 (Nat.Med. ;8(3) :225-32,2002)HIV 蛋白酶抑制剂如茚地那韦或沙奎那韦具有强效的抗血管生成活性和促进卡波西肉瘤的退化。

[0315] “血管生成抑制剂”是指无论采用何种机理,能抑制新血管的形成的化合物。血管生成抑制剂的实例包括但不限于 :酪氨酸激酶抑制剂如酪氨酸激酶受体 Flt-1(VEGFR1) 和 Flk-1/KDR(VEGFR20) 的抑制剂,表皮衍生的、成纤维细胞衍生的或血小板衍生的生长因子的抑制剂, MMP(基质金属蛋白酶) 抑制剂,整联蛋白阻断剂,干扰素 -α ,白介素 -12,多硫酸戊聚糖,环加氧酶抑制剂,包括非甾体抗炎药 (NSAID) 如阿司匹林和布洛芬以及选择性环加氧酶 -2 抑制剂如塞来昔布、伐地考昔 (valecoxib) 和罗非昔布,羧胺三唑,考布他汀 A-4,角鲨胺,6-O- 氯乙酰基 - 羰基)- 烟霉醇,沙利度胺,血管抑制素,肌钙蛋白 -1,血管紧张素 II 拮抗剂 (参见 Fernandez 等, J.Lab.Clin.Med.105 :141-145(1985)),以及 VEGF 抗体 (参见 Nature Biotechnology, Vol.17, pp.963-968(1999 年 10 月) ;Kim 等, Nature, 362,841-844(1993) ;WO 00/44777 ;和 WO 00/61186)。

[0316] 血管生成抑制剂的其他实例包括但不限于 :内皮抑素、ukrain、豹蛙酶、IM862、5- 甲氧基 -4-[2- 甲基 -3-(3- 甲基 -2- 丁烯基) 环氧乙烷基]-1- 氧杂螺 [2,5] 辛 -6- 基 (氯乙酰基) 氨基甲酸酯、乙酰基二苯胺 (acetyldinanaline)、5- 氨基 -1-[[3,5- 二氯 -4-(4- 氯苯甲酰基) 苯基]- 甲基]-1H-1,2,3- 三唑 -4- 甲酰胺、CM101、角鲨胺、考布他汀、RP14610、NX31838、硫酸化甘露戊糖磷酸盐、7,7-(羰基 - 双 [亚氨基 -N- 甲基 -4,2- 吡咯并羰基 - 亚氨基 [N- 甲基 -4,2- 吡咯]- 羰基亚氨基]- 双 -(1,3- 萘二磺酸盐) 以及 3-[(2,4- 二甲基吡咯 -5- 基) 亚甲基]-2- 吲哚啉酮 (SU5416)。

[0317] “细胞增殖和存活信号途径抑制剂”是指抑制细胞表面受体以及这些表面受体下游的信号转导级联的药剂。此类药剂包括 :EGFR 抑制剂的抑制剂 (例如吉非替尼和埃罗替尼)、ERB-2 抑制剂 (例如曲妥珠单抗)、IGFR 抑制剂、CD20 抑制剂 (利妥昔单抗)、细胞因子受体抑制剂、MET 抑制剂、PDK 抑制剂 (例如 LY294002)、丝氨酸 / 苏氨酸激酶、Raf 抑制剂 (例如 BAY-43-9006)、MEK 抑制剂 (例如 CI-1040 和 PD-098059) 以及 mTOR 抑制剂 (例如 Wyeth CCI-779 和 Ariad AP23573)。此类药剂包括小分子抑制剂化合物和抗体拮抗剂。

[0318] “细胞凋亡诱导剂”包括但不限于 TNF 受体家族成员 (包括 TRAIL 受体) 激活剂。

[0319] “干扰细胞周期检查点的药剂”是指抑制转导细胞周期检查点信号的蛋白激酶,从而使癌细胞对 DNA 损伤剂敏感的化合物。此类药剂包括 ATR、ATM 抑制剂, Chk1 和 Chk2 激酶以及 cdk 和 cdc 激酶抑制剂,并以 7- 羟基星形孢菌素、夫拉平度、CYC202(Cyclacel) 和 BMS-387032 具体示例。

[0320] “干扰受体酪氨酸激酶 (RTK) 的药剂”是指抑制 RTK 并因此抑制与肿瘤发生和肿瘤进展有关的机制的化合物。此类药剂包括但不限于酪氨酸激酶抑制剂,如 c-Kit、Eph、PDGF、Flt3、Lck、Btk 和 c-Met 的抑制剂。其他药剂包括如 Bume-Jensen 和 Hunter,2001, Nature 411 :355-365 所述的 RTK 抑制剂。“酪氨酸激酶抑制剂”的实例包括但不限于 :N-(三氟甲基苯基)-5- 甲基异噁唑 -4- 甲酰胺、3-[(2,4- 二甲基吡咯 -5- 基) 亚甲基) 吲哚啉 -2- 酮、17-(烯丙基氨基)-17- 去甲氧基格尔德霉素、4-(3- 氯 -4- 氟苯基氨基)-7- 甲氧基 -6-[3-(4- 吗啉基) 丙氧基]- 喹唑啉、N-(3- 乙炔基苯基)-6,7- 双 (2- 甲氧基乙氧基)-4- 喹啉胺、BIBX1382、2,3,9,10,11,12- 六氢 -10-(羟基甲基)-10- 羟基 -9- 甲

基-9,12-环氧-1H-二吲哚并[1,2,3-fg:3′,2′,1′-kl]吡咯并[3,4-i][1,6]苯并二氧杂环辛烷-1-酮、SH268、染料木黄酮、ST1571、CEP2563、4-(3-氯苯基氨基)-5,6-二甲基-7-H-吡咯并[2,3-d]嘧啶甲烷磺酸盐、4-(3-溴-4-羟基苯基)氨基-6,7-二甲氧基喹唑啉、4-(4′-羟基苯基)氨基-6,7-二甲氧基喹唑啉、SU6668、SU11248、STI571A、N-4-氯苯基-4-(4-吡啶基甲基)-1-酞嗪胺和EMD121974。

[0321] HDAC抑制剂还可用于与血小板纤维蛋白原受体(GP IIb/IIIa)拮抗剂如替罗非班联合使用,以抑制癌细胞的转移。肿瘤细胞主要通过凝血酶生成激活血小板。该激活与VEGF的释放相关。VEGF的释放通过在血管内皮粘附点处增加外渗而增强转移(Amirkhosravi,1999,Platelets 10:285-292)。因此,HDAC抑制剂与GP IIb/IIIa拮抗剂联合用于抑制转移。其他纤维蛋白原受体拮抗剂的实例包括阿昔单抗、依替巴肽、西拉非班、拉米非班、洛曲非班、色满非班和CT50352。

[0322] 如上所用的,“整联蛋白阻断剂”是指选择性地拮抗、抑制或对抗生理配体与$\alpha_v\beta_3$整联蛋白的结合的化合物,选择性地拮抗、抑制或对抗生理配体与$\alpha_v\beta_5$整联蛋白的结合的化合物,拮抗、抑制或对抗生理配体与$\alpha_v\beta_3$整联蛋白和$\alpha_v\beta_5$整联蛋白两者的结合的化合物,以及拮抗、抑制或对抗在毛细血管内皮细胞上表达的特定整联蛋白的活性的化合物。该术语还指$\alpha_v\beta_6$、$\alpha_v\beta_8$、$\alpha_1\beta_1$、$\alpha_2\beta_1$、$\alpha_5\beta_1$、$\alpha_6\beta_1$和$\alpha_6\beta_4$整联蛋白的拮抗剂。该术语还指$\alpha_v\beta_3$、$\alpha_v\beta_5$、$\alpha_v\beta_6$、$\alpha_v\beta_8$、$\alpha_1\beta_1$、$\alpha_2\beta_1$、$\alpha_5\beta_1$、$\alpha_6\beta_1$和$\alpha_6\beta_4$整联蛋白的任何组合的拮抗剂。

[0323] 与本文所公开的HDAC8选择性药剂联合使用的市售抗癌剂包括但不限于:阿巴瑞克(Plenaxis®)、阿地白介素(Prokine®)、阿地白介素(Proleukin®)、阿仑珠单抗(Campath®)、阿利维a酸(Panretin®)、别嘌醇(Zyloprim®)、六甲蜜胺(Hexalen®)、氨磷汀(Ethyol®)、阿那曲唑(Arimidex®)、三氧化二砷(Trisenox®)、门冬酰胺酶(Elspar®)、阿扎胞苷(Vidaza®)、贝伐珠单抗(Avastin®)、贝沙罗汀(Targretin®)、博来霉素(Blenoxane®)、硼替佐米(Velcade®)、白消安(Busulfex®)、白消安(Myleran®)、卡芦睾酮(Methosarb®)、卡培他滨(Xeloda®)、卡铂(Paraplatin®)、卡莫司汀(BCNU,BiCNU)、卡莫司汀(Gliadel®)、塞来昔布(Celebrex®)、西妥昔单抗(Erbitux®)、苯丁酸氮芥(Leukeran®)、顺铂(Platinol®)、克拉屈滨(Leustatin®)、氯法拉滨(Clolar®)、环磷酰胺(Cytoxan®)、阿糖胞苷(Cytosar-U®)、阿糖胞苷脂质体(DepoCyt)、达卡巴嗪(DTIC-Dome)、更生霉素(放线菌素D,Cosmegen®)、达依泊汀α(Aranesp®)、达沙替尼(Sprycel®)、柔红霉素脂质体(DanuoXome)、柔红霉素(道诺霉素,Daunorubicin®)、柔红霉素(道诺霉素,Cerubidine®)、地西他滨(Dacogen®)、地尼白介素(Ontak®)、右雷佐生(Zinecard®)、多西他赛(Taxotere®)、

多柔比星(Adriamycin®)、多柔比星脂质体(Doxil®)、丙酸屈他雄酮、表柔比星(Ellence®)、表柔比星、依泊汀α(EPOGEN®)、厄洛替尼(Tarceva®)、雌莫司汀(Emcyt®)、磷酸依托泊苷(Etopophos®)、依托泊苷(VP-16；Vepesid®)、依西美坦(AROMASIN®)、枸橼酸芬太尼(Fentora®)、非格司亭(Neupogen®)、氟尿苷(FUDR)、氟达拉滨(Fludara®)、氟尿嘧啶(5-FU，Adrucil®)、氟维司群(Faslodex®)、吉非替尼(Iressa®)、吉西他滨(Gemzar®)、吉妥珠单抗奥佐米星(Mylotarg®)、醋酸戈舍瑞林(Zoladex®)、醋酸组氨瑞林(Histrelin®)、羟基脲(Hydrea®)、替伊莫单抗(Zevalin®)、伊达比星(Idamycin®)、异环磷酰胺(IFEX®)、甲磺酸伊马替尼(Gleevec®)、干扰素α2a(Roferon®)、干扰素α-2b(Intron A®)、伊立替康(Camptosar®)、来那度胺(Revlimid®)、来曲唑(Femara®)、甲酰四氢叶酸(Leucovorin®)、醋酸亮丙瑞林(Eligard®)、左旋咪唑(Ergamisol®)、洛莫司汀(CCNUCeeBU®)、二氯甲基二乙胺(meclorethamine)(氮芥，Mustargen®)、醋酸甲地孕酮(Megace®)、美法仑(Alkeran®)、巯嘌呤(6-MP，Purinethol®)、美司钠(Mesnex®)、氨甲蝶呤(Rheumatrex®，Trexall®)、甲氧沙林(Uvadex®)、丝裂霉素C(Mutamycin®)、丝裂霉素C(Mitozytrex®)、米托坦(Lysodren®)、米托蒽醌(Novantrone®)、苯丙酸诺龙(Durabolin-50)、奈拉滨(Arranon®)、诺非单抗(Verluma®)、奥普瑞白介素(Neumega®)、奥沙利铂(Eloxatin®)、紫杉醇(Paxene®)、紫杉醇(Taxol®)、紫杉醇蛋白质结合颗粒(Abraxane®)、帕利夫明(Kepivance®)、帕米膦酸盐(Aredia®)、帕尼单抗(Vectibix®)、培加酶(Adagen®)、培门冬酶(Oncaspar®)、培非司亭(Neulasta®)、培美曲塞二钠(Alimta®)、喷司他丁(Nipent®)、哌泊溴烷(Vercyte®)、普卡霉素，光辉霉素(Mithracin®)、卟吩姆钠(Photofrin®)、丙卡巴肼(Matulane®)、奎纳克林(Atabrine®)、拉布立酶(Elitek®)、利妥昔单抗(Rituxan®)、沙格司亭(Leukine®)、沙格司亭(Prokine®)、索拉非尼(Nexavar®)、链佐星(Zanosar®)、马来酸舒尼替尼(Sutent®)、滑石(Sclerosol®)、他莫昔芬(Nolvadex®)、替莫唑胺(Temodar®)、替尼泊苷(VM-26，Vumon®)、睾内酯(Teslac®)、沙利度胺(Thalomid®)、硫鸟嘌呤(6-TG，Thioguanine®

)、噻替哌(Thioplex®)、托泊替康(Hycamtin®)、托瑞米芬(Fareston®)、托西莫单抗(Bexxar®)、托西莫单抗/I-131托西莫单抗(Bexxar®)、曲妥珠单抗(Herceptin®)、维甲酸(ATRA,Vesanoid®)、尿嘧啶氮芥、戊柔比星(Valstar®)、长春碱(Velban®)、长春新碱(Oncovin®)、长春瑞滨(Navelbine®)、伏林司他(Zolinza®)、唑来膦酸盐(Zometa®)和唑来膦酸(Zometa®)。

[0324] 在一些实施方案中,本文所述的HDAC8选择性化合物与基因疗法联合使用以治疗癌症。关于治疗癌症的遗传策略的综述参见Hall等(Am J Hum Genet 61:785-789,1997)和Kufe等(Cancer Medicine,5th Ed,pp 876-889,BC Decker,Hamilton 2000)。基因疗法用来递送任何肿瘤抑制基因。此类基因的实例包括但不限于:通过重组病毒介导的基因转移进行递送的p53、Duc-4、NF-I、NF-2、RB、WT1、BRCA1、BRCA2、uPA/uPAR拮抗剂("Adenoviras-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice,"Gene Therapy,August 1998,5(8):1105-13),以及干扰素-γ(J.Immunol.2000;164:217-222)。

[0325] 在其他实施方案中,本文所述的HDAC8选择性化合物与固有的多药抗药性(MDR)的抑制剂,特别是与运转蛋白的高表达水平相关的MDR的抑制剂联合施用。此类MDR抑制剂包括p-糖蛋白(P-gp)的抑制剂,诸如LY335979、XR9576、OC144-093、R101922、VX853和PSC833(伐司朴达)。

[0326] 在一些实施方案中,本文所述的HDAC8选择性化合物与止吐剂结合使用,以治疗由本文所述的HDAC8选择性化合物单独使用或与放射疗法联合使用导致的恶心或呕吐,包括急性、延迟、后期和预期的呕吐。对于呕吐的预防或治疗,本文所述的HDAC8选择性化合物与止吐剂结合使用,该止吐药剂例如但不限于:神经激肽-1受体拮抗剂、5HT3受体拮抗剂(如昂丹司琼、格拉司琼、托烷司琼、帕洛诺司琼和扎托司琼(zatisetron))、$GABA_B$受体激动剂(诸如巴氯芬)、皮质类固醇(如地塞米松、泼尼松、泼尼松龙)、多巴胺拮抗剂(例如但不限于多潘立酮、氟哌利多、氟哌啶醇、氯丙嗪、异丙嗪、丙氯拉嗪、甲氧氯普胺)、抗组胺药(H1组胺受体拮抗剂,例如但不限于赛克力嗪、苯海拉明、茶苯海明、氯苯甲嗪、异丙嗪、羟嗪)、大麻酚类(例如但不限于印度大麻、屈大麻酚、卓那比醇)和其他(例如但不限于曲美苄胺、生姜、愈吐宁定、丙泊酚)。

[0327] 在一个实施方案中,选自神经激肽-1受体拮抗剂、5HT3受体拮抗剂和皮质类固醇的止吐剂作为佐药施用以用于治疗或预防由施用该化合物导致的呕吐。

[0328] 在其他实施方案中,本文所述的HDAC8选择性化合物与可用于治疗贫血的药剂联合施用。此类贫血治疗剂是,例如,连续的红细胞生成受体活化剂(如依泊汀-α)。

[0329] 在其他实施方案中,本文所述的HDAC8选择性化合物与可用于治疗中性粒细胞减少症的药剂联合施用。可用于治疗中性粒细胞减少症的药剂的实例包括但不限于调节中性粒细胞的产生和功能的造血生长因子,如人粒细胞集落刺激因子(G-CSF)。G-CSF的实例包括非格司亭。

[0330] 在一些实施方案中,本文所述的选择性HDAC8与诸如左旋咪唑、卡介苗、奥曲肽、异丙肌苷和日达仙(Zadaxin)的免疫增强药联合施用。

[0331] 在其他实施方案中，本文所述的HDAC8选择性化合物与双磷酸盐（应理解为包括双磷酸盐、二磷酸盐、双磷酸和二磷酸）联合可用于治疗或预防癌症，包括骨癌。双磷酸盐的实例包括但不限于：羟乙膦酸盐(Didronel®)、帕米膦酸盐(Aredia®)、阿屈膦酸盐(Fosamax®)、利塞膦酸盐(Actonel®)、唑来膦酸盐(Zometa®)、伊班膦酸盐(Boniva®)、伊卡膦酸盐或英卡膦酸盐（cimadronate）、氯屈膦酸盐、EB-1053、米诺膦酸盐、奈立膦酸盐、吡磷酸盐和替鲁膦酸盐，包括其任何和所有的药学上可接受的盐、衍生物、水合物及混合物。

[0332] 在其他实施方案中，本文所述的HDAC8选择性化合物与芳香酶抑制剂联合可用于治疗乳腺癌。芳香酶抑制剂的实例包括但不限于：阿那曲唑、来曲唑和依西美坦。

[0333] 在一些实施方案中，本文所述的HDAC8选择性化合物与siRNA或RNAi疗法联合可用于治疗或预防癌症。

[0334] “DNA甲基转移酶抑制剂”是指通过DNA甲基转移酶抑制DNA碱基胞嘧啶在该碱基的C-5位上的甲基化的化合物。在一些实施方案中，DNA甲基转移酶抑制剂包括5-氮胞嘧啶和zebularine®。

放射治疗

[0335] 放射疗法亦被称为放射治疗，是用电离辐射对癌症和其他疾病的治疗。电离辐射聚集能量，该能量通过破坏受治疗区（“靶组织”）内的细胞的遗传物质而损伤或破坏该细胞，使这些细胞不能继续生长。虽然辐射对癌细胞和正常细胞都造成损伤，但是后者能够更好地适当地自我修复和功能修复。放射疗法用于治疗局部的实体瘤，如皮肤癌、舌癌、喉癌、脑癌、乳腺癌、前列腺癌、结肠癌、子宫癌和/或子宫颈癌。它还用于治疗白血病和淋巴瘤（分别是血液形成细胞和淋巴系统的癌症）。

[0336] 一种用于向癌细胞传送辐射的技术是直接将放射性植入物放置于肿瘤或体腔中。这被称为内部放射疗法（近距离放射疗法、间质内照射和腔内照射是内部放射疗法的类型）。使用内部放射疗法，放射剂量集中在小区域内，并且患者在医院留住数日。内部放射疗法常用于舌癌、子宫癌、前列腺癌、结肠癌和子宫颈癌。

[0337] 术语“放射疗法”或“电离辐射”包括所有形式的辐射，包括但不限于α、β和γ辐射和紫外线。使用或不使用同时或序贯化疗的放射疗法对头颈癌、乳腺癌、皮肤癌、肛门生殖器癌以及诸如瘢痕疙瘩、硬纤维瘤、血管瘤、动静脉畸形和组织细胞增多症X等一些非恶性疾病是有效的方式。

[0338] 本文提供了使用至少一种组蛋白脱乙酰酶抑制剂来减少由至少一种其他治疗性处置引起的副作用（诸如辐射诱发的正常组织纤维化或化疗诱发的组织坏死）的方法，本文还提供了与放射疗法和其他抗癌剂协同抑制肿瘤细胞生长的方法。

生长激素促泌素 (Secretagogues)

[0339] 在一些实施方案中，HDAC8的选择性抑制剂与一种或多种生长激素促泌素联合使用，该生长激素促泌素包括但不限于：精氨酸、L-3,4-二羟基苯丙氨酸(1-多巴)、胰高血糖素、加压素、PACAP(垂体腺苷酸环化酶激活肽)、毒蕈碱受体激动剂和合成六肽、GHRP(生长激素释放肽)。

用于治疗自身免疫性疾病、炎性疾病或变态反应疾病的药剂

[0340] 在受试者患有自身免疫性疾病、炎性疾病或变态反应疾病或具有患该疾病的风险的一个实施方案中，选择性 HDAC8 抑制剂化合物与一种或多种下列治疗剂任意联合施用：免疫抑制剂（例如，他克莫司、环孢菌素、雷帕霉素、氨甲蝶呤、环磷酰胺、硫唑嘌呤、巯嘌呤、霉酚酸酯或 FTY720）、糖皮质激素类（例如，强的松、醋酸可的松、泼尼松龙、甲泼尼龙、地塞米松、倍他米松、曲安西龙、倍氯米松、醋酸氟氢可的松、醋酸脱氧皮质酮、醛固酮）、非甾体抗炎药（例如，水杨酸盐、芳基链烷酸、2- 芳基丙酸、N- 芳基氨茴酸、昔康类、昔布类或硫酰替苯胺类）、Cox-2 特异性抑制剂（例如，伐地考昔、塞来昔布或罗非昔布）、来氟米特、硫化葡糖金、硫代苹果酸金、金诺分、柳氮磺胺吡啶、羟基氯喹、米诺环素、TNF-α 结合蛋白质（例如，英利昔单抗、依那西普或阿达木单抗）、阿巴西普、阿那白滞素、干扰素 -β、干扰素 -γ、白介素 -2、变态反应疫苗、抗组胺药、抗白三烯、β- 激动剂、茶碱或抗胆碱能药。

[0341] 在一个实施方案中，本文所述的选择性 HDAC8 抑制剂化合物，或含有本文所述的选择性 HDAC8 抑制剂化合物的组合物和药物与抗炎药联合向患者施用，该抗炎药包括但不限于非甾体抗炎药 (NSAID) 和皮质类固醇（糖皮质激素）。

[0342] NSAID 包括但不限于：阿司匹林、水杨酸、龙胆酸、胆碱水杨酸镁、水杨酸胆碱、胆碱水杨酸镁、水杨酸胆碱、水杨酸镁、水杨酸钠、二氟尼柳、卡洛芬、非诺洛芬、非诺洛芬钙、氟比洛芬、布洛芬、酮洛芬、纳布美通、酮咯酸、酮咯酸氨丁三醇、萘普生、奥沙普秦、双氯芬酸、依托度酸、吲哚美辛、舒林酸、托美丁、甲氯芬那酸盐、甲氯芬那酸钠、甲芬那酸、吡罗昔康、美洛昔康、COX-2 特异性抑制剂（例如但不限于：塞来昔布、罗非昔布、伐地考昔、帕瑞考昔、艾托考昔、CS-502、JTE-522、L-745，337 和 NS398）。

[0343] 本文设想了与作为选择性 COX-2 抑制剂的 NSAID 的组合。

[0344] 已被描述为选择性 COX-2 抑制剂且因此在本文所述的方法和药物组合物中有用的化合物包括但不限于：塞来昔布、罗非昔布、芦米考昔、依托考昔、伐地考昔和帕瑞考昔，或其药学上可接受的盐。

[0345] 皮质类固醇包括但不限于：倍他米松、强的松、阿氯米松、醛固酮、安西奈德、倍氯米松、倍他米松、布地奈德、环索奈德、氯倍他索、氯倍他松、氯可托龙、氯泼尼醇、可的松、可的伐唑、地夫可特、脱氧皮质酮、地奈德、去羟米松、去氧皮质酮、地塞米松、二氟拉松、二氟可龙、二氟泼尼酯、氟氯缩松、氟氢可的松、氟氢缩松、氟米松、氟尼缩松、氟轻松、醋酸氟轻松、氟可丁、氟可龙、氟米龙、氟培龙、氟泼尼定、氟替卡松、福莫可他、哈西奈德、卤米松、氢化可的松 / 皮质醇、醋丙氢化可的松、丙丁酸氢化可的松、丁酸氢化可的松、氯替泼诺、甲羟松、甲泼尼松、甲基泼尼松龙、醋丙甲泼尼龙、糠酸莫米松、帕拉米松、泼尼卡酯、强的松 / 泼尼松龙、利美索龙、替可的松、曲安西龙和乌倍他索。

[0346] 在一个实施方案中，HDAC8 选择性抑制剂与白三烯受体拮抗剂联合施用，该白三烯受体拮抗剂包括但不限于：BAY u9773，Cuthbert 等，EP 00791576（公开于 1997 年 8 月 27 日）；DUO-LT(Tsuji 等，Org.Biomol.Chem.，1，3139-3141，2003)，扎鲁司特(Accolate®)，孟鲁司特(Singulair®)，普仑司特 (prankulast) (Onon®)，及其衍生物或类似物。

试剂盒 / 制品

[0347] 为了在本文所述的治疗性应用中使用，本文还描述了试剂盒和制品。此类试剂盒可以包括载体、包装或容器，其被分隔以接纳一个或多个容器如小瓶、管等，各个容器包含

将在本文所述的方法中使用的一种单独的元件。合适的容器包括，例如瓶子、小瓶、注射器和试管。容器由诸如玻璃或塑料等多种材料构成。

[0348] 本文提供的制品包含包装材料。药物包装材料的实例包括但不限于泡罩包装、瓶子、管、吸入器、泵、袋、小瓶、容器、注射器、瓶子和适合所选制剂和预期的给药和治疗模式的任何包装材料。大量本文提供的化合物和组合物的制剂被考虑作为对任何受益于 HDAC 活性的抑制或其中 HDAC 是症状或病因的介质或贡献者的疾病、病症或状况的多种治疗。

[0349] 例如，容器包括一种或多种本文所述的化合物，任选地在组合物中或与另一种如本文公开的药剂组合。容器任选地具有无菌进入口（例如，是静脉内溶液袋或带有可被皮下注射针头刺穿的塞子的小瓶的容器）。此类试剂盒任选地包含化合物，以及关于其在本文所述的方法中的应用的识别性说明或标签或说明书。

[0350] 试剂盒将包括一个或多个额外的容器，各个容器含有从商业和使用者的角度期望用于本文所述化合物的各种材料中的一种或多种（例如试剂，任选地以浓缩形式，和 / 或装置）。此类材料的非限制性实例包括但不限于缓冲液、稀释剂、过滤器、针头、注射器；托架 (carrier)、包装、容器、小瓶和 / 或管标签——该标签列出了内容物和 / 或使用说明，以及带有使用说明的包装插入物。也将包括一套说明书。

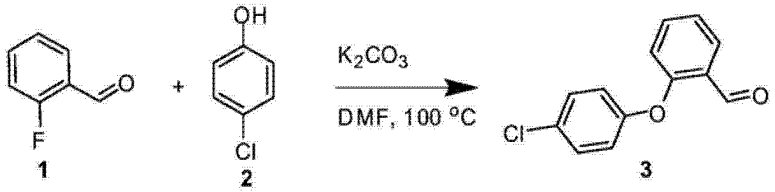
[0351] 标签附着在容器上或与容器相关联。当构成标签的字母、数字或其它字符附着、模塑或铭刻于容器自身时，该标签附着在容器上；当标签存在于同样支撑容器的托座或托架内时，例如作为包装插入物，该标签与容器相关联。标签用来指示内容物将用于特定的治疗性应用。标签还指示内容物的使用说明，例如在本文所述的方法中的使用说明。

[0352] 在某些实施方案中，药物组合物在包装或分配器装置中提供，该包装或分配器包含一个或多个包含本文提供的化合物的单位剂型。例如，包装包含金属箔或塑料薄膜，例如泡罩包装。包装或分配器装置附有给药说明书。包装或分配器还附有与容器相关联的、作为管理药物制造、使用或销售的政府机构所规定的形式的通知，该通知反映出该药物形式被该机构批准用于人或兽医给药。例如，这样的通知是经美国食品和药品管理局批准用于处方药的标签，或批准的产品插入物。还制备在相容的药物载体中配制的包含本文提供的化合物的组合物，将其放置在适当容器中，并标注用于治疗所指出的病症。

实施例

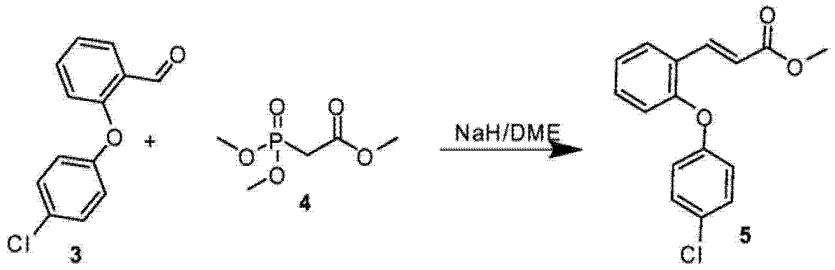
[0353] 这些实施例仅为了说明的目的而提供，并不限定本文提供的权利要求的范围。用于合成本文所述化合物的起始材料和试剂是合成的或获自商业来源，如 Sigma-Aldrich、Fluka、Acros Organics、Alfa Aesar、Bachem 等。

实施例 1：(E)-3-(2-(4- 氯苯氧基）苯基）-N- 羟基丙烯酰胺 (6) 的合成

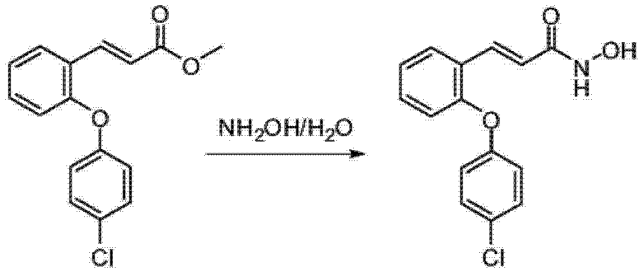


[0354] 步骤 1：2- 氟 - 苯甲醛 (1，7.0g，56.4mmol)、4- 氯苯酚 (2，7.25g，56.4mmol) 与 K_2CO_3(12.0g，85mmol) 在 50mL DMF 中的混合物于 100℃加热过夜。通过 LC/MS 监测反应进程。反应完成后，将反应混合物冷却，倒入水 (30mL) 中，然后用 EtOAc 萃取两次。将 EtOAc

层合并，用水洗涤，继而用盐水洗涤，并经 $MgSO_4$ 干燥。过滤和浓缩后，通过急骤层析（己烷/EtOAc：0-100%）纯化粗物质，得到 9.0g(69%产率)2-(4-氯苯氧基）苯甲醛 (3)。

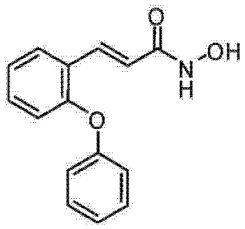


[0355] 步骤 2：向 2-(4-氯苯氧基）苯甲醛 (3,0.5g,2.15mmol) 和膦酰基乙酸三甲酯 (4,0.47g,2.6mmol) 在 20mL DMF 中的溶液中加入 NaH(95%)(62mg,2.6mmol)。该混合物在 100℃下搅拌过夜。将 DME 蒸发，然后加水以猝灭该反应，并用 EtOAc 萃取两次。将 EtOAc 层合并，用水洗涤，然后用盐水洗涤，并经 $MgSO_4$ 干燥。过滤和浓缩后，分离得到 0.57g(90%产率：经 UV254 测定＞ 90%纯度)(E)-3-(2-(4-氯苯氧基）苯基）丙烯酸甲酯 (5)，并且无需进一步纯化而使用。



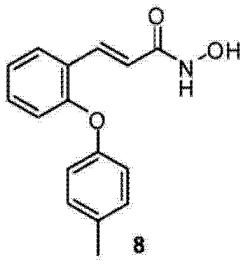
[0356] 步骤 3：向冷却的 (E)-3-(2-(4-氯苯氧基）苯基）丙烯酸甲酯 (5,0.29g,1.0mmol) 在 IPA(5mL) 中的溶液中加入 50% NH_2OH/H_2O(1.0g,30mmol)，然后加入 1N NaOH(2mmol,2mL)。该反应混合物在 0℃下搅拌 1hr，随后酸化至 pH ＝ 7，用水进行稀释，继而用 EtOAc(3X50mL) 萃取。合并的有机层用盐水洗涤并经 $MgSO_4$ 干燥。过滤和蒸发后，分离得到 0.24g(84%产率)(E)-3-(2-(4-氯苯氧基）苯基）-N-羟基丙烯酰胺 (6)。粗物质经 HPLC 纯化。EM（计算）：289.05；MS(M+1H) ＝ 290.0。

实施例 2：(E)-N-羟基 -3-(2-苯氧基苯基）丙烯酰胺 (7) 的合成



[0357] 如实施例 1 中所述合成标题化合物。EM（计算）：255.09；MS(M+1H) ＝ 256.5。

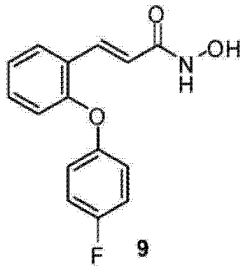
实施例 3：(E)-3-(2-(对甲苯氧基）苯基）-N-羟基丙烯酰胺 (8) 的合成



8

[0358] 如实施例 1 中所述合成标题化合物。EM(计算) :269.11 ;MS(M+1H) = 270.5。

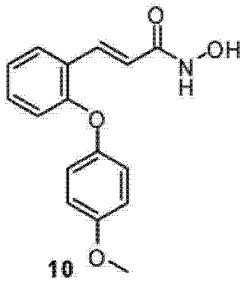
实施例 4 :(E)-3-(2-(4- 氟苯氧基) 苯基)-N- 羟基丙烯酰胺 (9) 的合成



9

[0359] 如实施例 1 中所述合成标题化合物。EM(计算) :273.08 ;MS(M+1H) = 274.0。

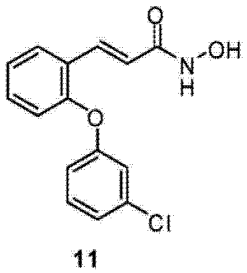
实施例 5 :(E)-N- 羟基 -3-(2-(4- 甲氧基苯氧基) 苯基) 丙烯酰胺 (10) 的合成



10

[0360] 如实施例 1 中所述合成标题化合物。EM(计算) :285.1 ;MS(M+1H) = 286.0。

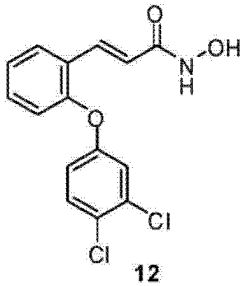
实施例 6 :(E)-3-(2-(3- 氯苯氧基) 苯基)-N- 羟基丙烯酰胺 (11) 的合成



11

[0361] 如实施例 1 中所述合成标题化合物。EM(计算) :289.05 ;MS(M+1H) = 290.0。

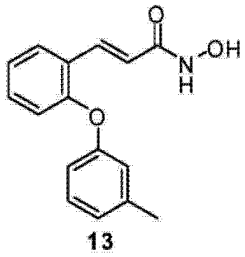
实施例 7 :(E)-3-(2-(3,4- 二氯苯氧基) 苯基)-N- 羟基丙烯酰胺 (12) 的合成



12

[0362] 如实施例 1 中所述合成标题化合物。EM(计算) :323.01 ;MS(M+1H) = 324.5。

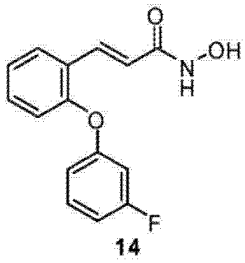
实施例 8 :(E)-N- 羟基 -3-(2-(间甲苯氧基) 苯基) 丙烯酰胺 (13) 的合成



13

[0363] 如实施例 1 中所述合成标题化合物。EM(计算) :269.11 ;MS(M+1H) = 270.5。

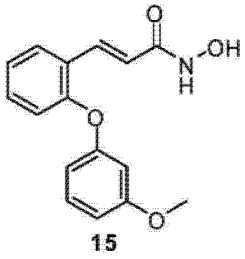
实施例 9 :(E)-3-(2-(3- 氟苯氧基) 苯基)-N- 羟基丙烯酰胺 (14) 的合成



14

[0364] 如实施例 1 中所述合成标题化合物。EM(计算) :273.08 ;MS(M+1H) = 274.0。

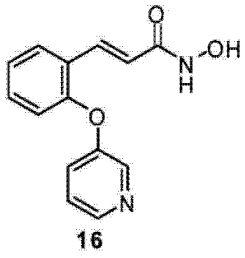
实施例 10 :(E)-N- 羟基 -3-(2-(3- 甲氧基苯氧基) 苯基) 丙烯酰胺 (15) 的合成



15

[0365] 如实施例 1 中所述合成标题化合物。EM(计算) :285.1 ;MS(M+1H) = 286.5。

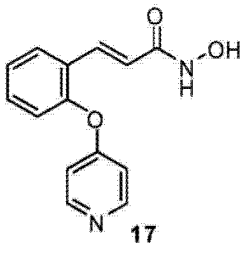
实施例 11 :(E)-N- 羟基 -3-(2-(吡啶 -3- 基氧基) 苯基) 丙烯酰胺 (16)



16

[0366] 如实施例 1 中所述合成标题化合物。EM(计算) :256.08 ;MS(M+1H) = 257.5。

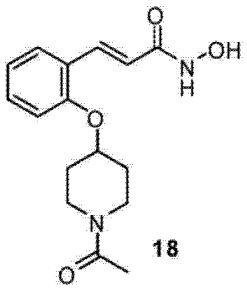
实施例 12 :(E)-N- 羟基 -3-(2-(吡啶 -4- 基氧基) 苯基) 丙烯酰胺 (17) 的合成



17

[0367] 如实施例 1 中所述合成标题化合物。EM(计算) :256.08 ;MS(M+1H) = 257.5。

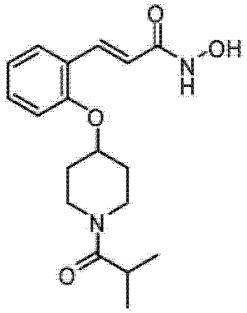
实施例 13 :(E)-3-(2-(1- 乙酰基哌啶 -4- 基氧基) 苯基)-N- 羟基丙烯酰胺 (18) 的合成



18

[0368] 如实施例 1 中所述合成标题化合物。EM(计算) :304.14 ;MS(M+1H) = 305.5。

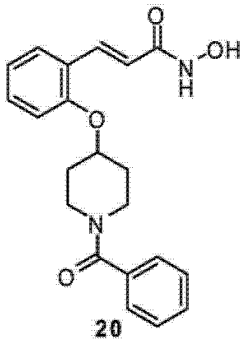
实施例 14 :(E)-N- 羟基 -3-(2-(1- 异丁酰基哌啶 -4- 基氧基) 苯基) 丙烯酰胺 (19) 的合成



19

[0369] 如实施例 1 中所述合成标题化合物。EM(计算) :332.17 ;MS(M+1H) = 333.5。

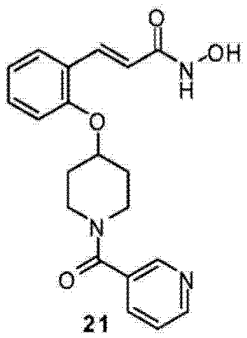
实施例 15 :(E)-3-(2-(1- 苯甲酰基哌啶 -4- 基氧基) 苯基)-N- 羟基丙烯酰胺 (20) 的合成



20

[0370] 如实施例 1 中所述合成标题化合物。EM(计算) :366.16 ;MS(M+1H) = 367.0。

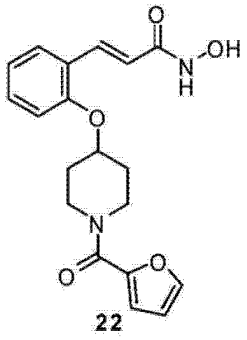
实施例 16 :(E)-N- 羟基 -3-(2-(1- 烟酰基哌啶 -4- 基氧基) 苯基) 丙烯酰胺 (21) 的合成



21

[0371] 如实施例 1 中所述合成标题化合物。EM(计算) :367.15 ;MS(M+1H) = 368.0。

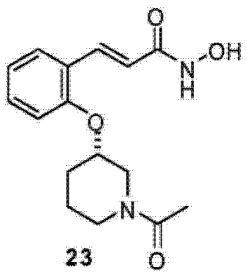
实施例 17 :(E)-3-(2-(1-(呋喃 -2- 羰基) 哌啶 -4- 基氧基) 苯基)-N- 羟基丙烯酰胺 (22) 的合成



22

[0372] 如实施例 1 中所述合成标题化合物。EM(计算) :356.14 ;MS(M+1H) = 357.0。

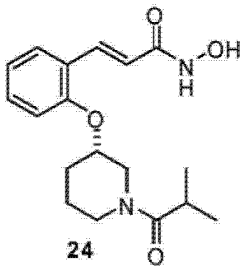
实施例 18 :(S,E)-3-(2-(1- 乙酰基哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺 (23) 的合成



23

[0373] 如实施例 1 中所述合成标题化合物。EM(计算) :304.14 ;MS(M+1H) = 305.5。

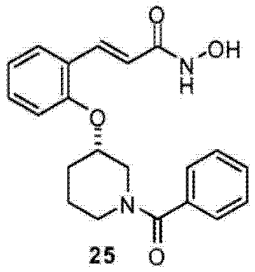
实施例 19 :(S,E)-N- 羟基 -3-(2-(1- 异丁酰基哌啶 -3- 基氧基) 苯基) 丙烯酰胺 (24) 的合成



24

[0374] 如实施例 1 中所述合成标题化合物。EM(计算) :332.17 ;MS(M+1H) = 333.5。

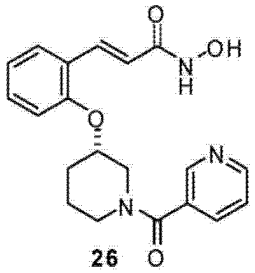
实施例 20 :(S, E)-3-(2-(1- 苯甲酰基哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺 (R, E)-3-(2-(1- 苯甲酰基哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺 (25) 的合成



25

[0375] 如实施例 1 中所述合成标题化合物。EM(计算) :366.16 ;MS(M+1H) = 367.0。

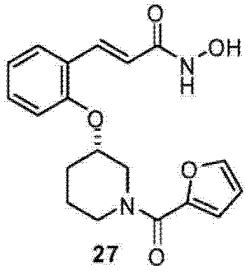
实施例 21 :(S, E)-N- 羟基 -3-(2-(1- 烟酰基哌啶 -3- 基氧基) 苯基) 丙烯酰胺 (26) 的合成



26

[0376] 如实施例 1 中所述合成标题化合物。EM(计算) :367.15 ;MS(M+1H) = 368.5。

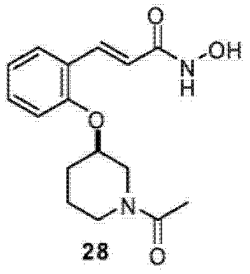
实施例 22 :(S,E)-3-(2-(1-(呋喃 -2- 羰基) 哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺 (27) 的合成



27

[0377] 如实施例 1 中所述合成标题化合物。EM(计算) :356.14 ;MS(M+1H) = 357.5。

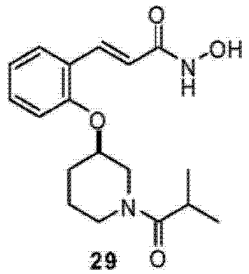
实施例 23 :(R,E)-3-(2-(1- 乙酰基哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺 (28) 的合成



28

[0378] 如实施例 1 中所述合成标题化合物。EM(计算) :304.14 ;MS(M+1H) = 305.5。

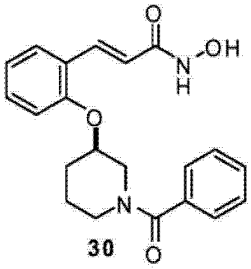
实施例 24 :(R,E)-N- 羟基 -3-(2-(1- 异丁酰基哌啶 -3- 基氧基) 苯基) 丙烯酰胺 (29) 的合成



29

[0379] 如实施例 1 中所述合成标题化合物。EM(计算) :332.17 ;MS(M+1H) ＝ 333.5。

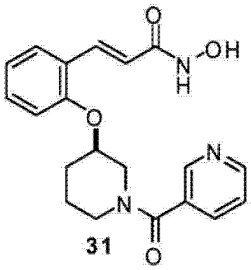
实施例 25 :(R,E)-3-(2-(1- 苯甲酰基哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺 (30) 的合成



30

[0380] 如实施例 1 中所述合成标题化合物。EM(计算) :366.16 ;MS(M+1H) ＝ 367.0。

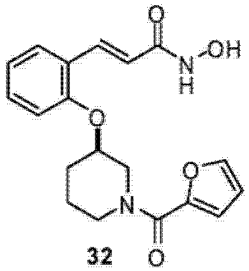
实施例 26 :(R, E)-N- 羟基 -3-(2-(1- 烟酰基哌啶 -3- 基氧基) 苯基) 丙烯酰胺 (31) 的合成



31

[0381] 如实施例 1 中所述合成标题化合物。EM(计算) :367.15 ;MS(M+1H) ＝ 368.0。

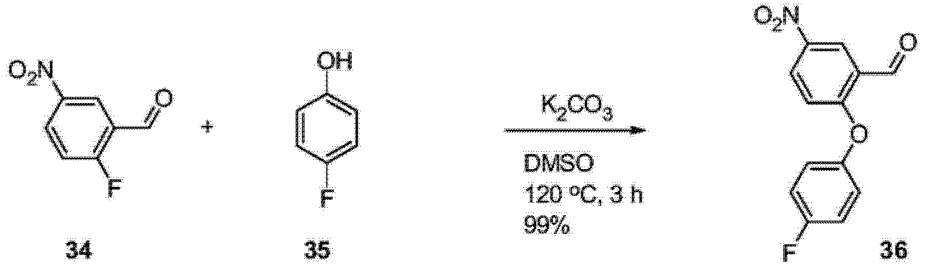
实施例 27 :(R,E)-3-(2-(1-(呋喃 -2- 羰基) 哌啶 -3- 基氧基) 苯基)-N- 羟基丙烯酰胺 (32) 的合成



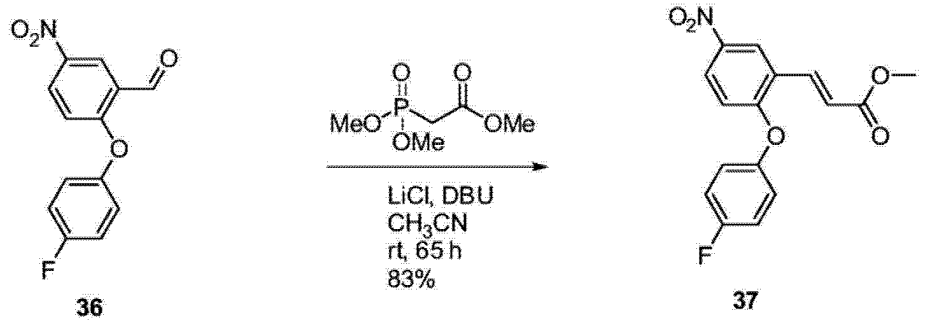
32

[0382] 如实施例 1 中所述合成标题化合物。EM(计算) :356.14 ;MS(M+1H) ＝ 357.5。

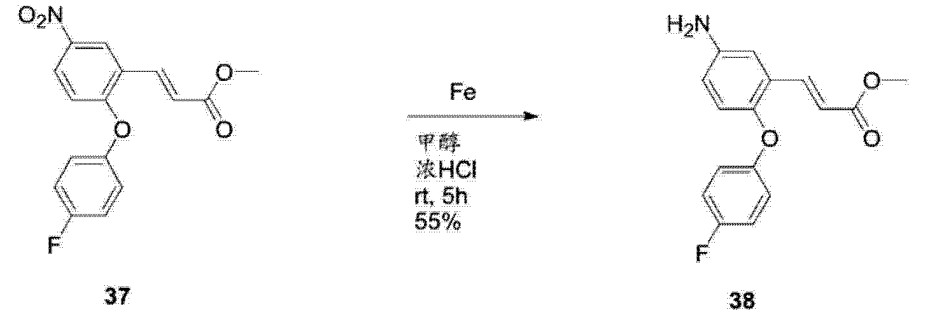
实施例 28 :(E)-N-(4-(4- 氟苯氧基)-3-(3-(羟基氨基)-3- 氧代丙 -1- 烯基) 苯基) 烟酰胺 (33) 的合成



[0383] 步骤 1 :在室温下,向 2- 氟 -5- 硝基 - 苯甲醛 (34)(676mg,4.0mmol) 和 4- 氟苯酚 (35)(537mg,4.8mmol) 在 DMSO(5mL) 中的溶液中加入 K_2CO_3(1.10g,8.0mmol)。所得混合物用 N_2 进行吹洗并在密封的容器中在 120℃下搅拌加热 3h。反应混合物冷却至室温并倒入至盐水中后,用乙酸乙酯 (35mLx3) 萃取该混合物。合并的萃取物用盐水 (10mL x2) 洗涤,经无水 $MgSO_4$ 干燥,过滤,并蒸发至干。残余物经 SiO_2 柱塞 (用己烷中的 15% EtOAc 洗脱) 纯化,得到呈粘稠的油的纯 2-(4- 氟 - 苯氧基)-5- 硝基 - 苯甲醛 (36)(1.05g,4.0mmol,99%)。ESI MS m/z262.2(M+H)$^+$。

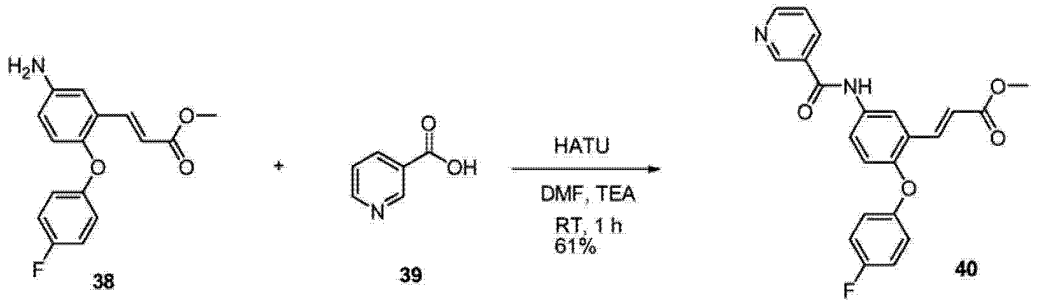


[0384] 步骤 2 :在室温下,向 2-(4- 氟 - 苯氧基)-5- 硝基 - 苯甲醛 (36)(469mg,1.79mmol) 和膦酰基乙酸三甲酯 (650mg,3.58mmol) 在乙腈 (20mL) 中的搅拌溶液中加入 LiCl(228mg,5.36mmol),随后加入 DBU(0.802mL,5.36mmol)。在室温下搅拌所得混合物 65h。减压浓缩该反应混合物后,残余物用乙酸乙酯 (100mL) 进行处理。EtOAc 溶液用 1M HCl 水溶液 (10mL x2)、饱和 $NaHCO_3$ 水溶液 (10mL) 和盐水 (10mL) 洗涤,经无水 $MgSO_4$ 干燥,过滤,并蒸发至干。残余物经 SiO_2 柱塞 (用己烷中的 10% 至 25% EtOAc 洗脱) 纯化,得到呈粘稠的油的纯 3-[2-(4- 氟 - 苯氧基)-5- 硝基 - 苯基]- 丙烯酸甲酯 (37)(478mg,1.50mmol,83%)。ESI MS m/z318.3(M+H)$^+$。

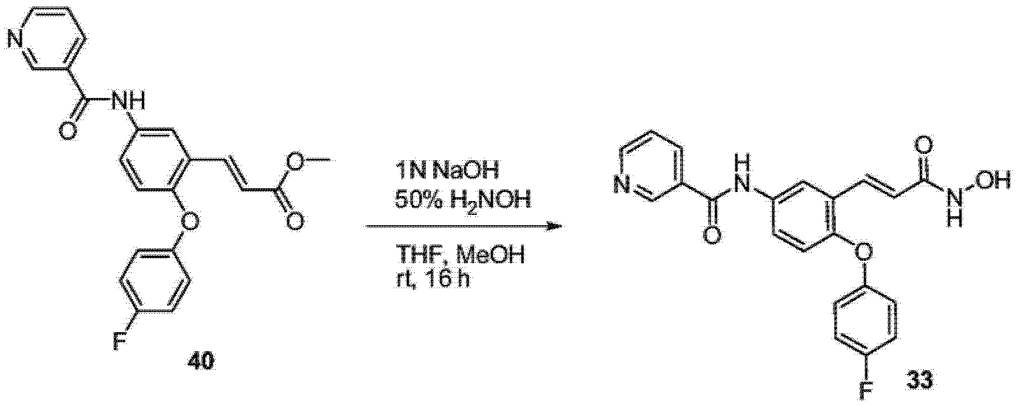


[0385] 步骤 3 :向 3-[2-(4- 氟 - 苯氧基)-5- 硝基 - 苯基]- 丙烯酸甲酯 (37)(478mg,1.50mmol) 在甲醇 (10mL) 中的搅拌溶液中加入 412mg(7.5mmol) 铁粉。在室温下,向该混合物中加入 10mL 浓 HCl。在室温下搅拌所得混合物 5h,然后静置 1h。该反应混合物经布氏漏斗过滤以除去铁粉,并将所得溶液蒸发至干。然后用乙酸乙酯处理,并用碳酸氢钠

水溶液和稀 HCl 洗涤。分离有机层并用 EtOAc(30mL x3) 进一步萃取水层。合并的有机相用盐水 (10mL x2) 洗涤，经无水 $MgSO_4$ 干燥，过滤，并蒸发至干。分离得到呈黄色油的 3-[2-(4- 氟 - 苯氧基)-5- 氨基 - 苯基]- 丙烯酸甲酯 (38)，且其无需进一步纯化而使用。ESI MS m/z 288.3$(M+H)^+$。



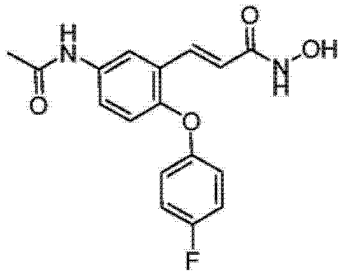
[0386] 步骤 4 :在室温和 N_2 下，向 3-[2-(4- 氟 - 苯氧基)-5- 氨基 - 苯基]- 丙烯酸甲酯 (38)(58mg,0.20mmol) 和 3- 吡啶甲酸 (39)(35mg,0.32mmol) 在 DMF(2mL) 中的搅拌溶液中加入 HATU(114mg,0.30mmol)，随后加入 TEA 溶液 (0.033mL,0.32mmol)。搅拌所得混合物 4h。减压浓缩该反应混合物后，残余物用乙酸乙酯 (75mL) 处理。溶液用酸 (HCl) 和碱 ($NaHCO_3$) 和盐水 (10mL x2) 洗涤，经无水 $MgSO_4$ 干燥，过滤，并蒸发至干。残余物经 SiO_2 柱塞 (用己烷中的 33％至 50％ EtOAc 洗脱) 纯化，得到呈粘稠的油的 3-{2-(4- 氟 - 苯氧基)-5-[(吡啶 -3- 羰基)- 氨基]- 苯基 }- 丙烯酸甲酯 (40)(47mg,0.12mmol,61％)。ESI MS m/z393.4$(M+H)^+$。



[0387] 步骤 5 :在室温下，向 3-{2-(4- 氟 - 苯氧基)-5-[(吡啶 -3- 羰基)- 氨基]- 苯基 }- 丙烯酸甲酯 (40)(86mg,0.22mmol) 在 THF(1.2mL) 和 MeOH(1.2mL) 中的搅拌溶液中加入 50％ NH_2OH 水溶液 (0.73mL,11mmol) 和 1N NaOH 水溶液 (0.5mL,0.5mmol)。在室温下搅拌所得混合物 16h。减压浓缩该反应混合物后，得到的水性悬浮液用 DMSO(1.5mL) 稀释并经 HPLC 纯化，得到呈白色固体的 N-[4-(4- 氟 - 苯氧基)-3-(2- 羟基氨基甲酰基 - 乙烯基)- 苯基]- 烟酰胺 (33)(54mg,0.14mmol,62％)。EM(计算) :393.37 ;ESI MS m/z394.1$(M+H)^+$。

实施例 29 :(E)-3-(5- 乙酰氨基 -2-(4- 氟苯氧基) 苯基)-N- 羟基丙烯酰胺 (41) 的合成

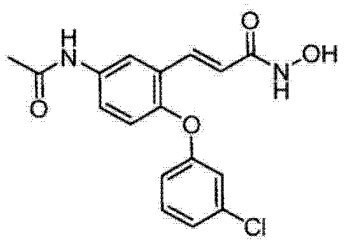
[0388] 如实施例 28 中所述合成标题化合物。EM(计算) :330.1 ;MS(M+1H) = 331.0。



41

实施例 30 :(E)-3-(5- 乙酰氨基 -2-(3- 氯苯氧基) 苯基)-N- 羟基丙烯酰胺 (42) 的合成

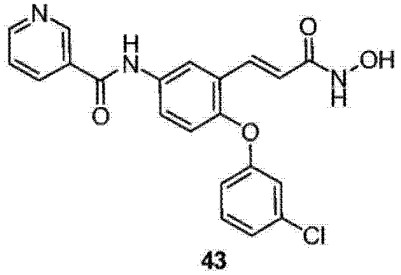
[0389] 如实施例 28 中所述合成标题化合物。EM(计算) :346.07 ;MS(M+1H) = 347.0。



42

实施例 31 :(E)-N-(4-(3- 氯苯氧基)-3-(3-(羟基氨基)-3- 氧代丙 -1- 烯基) 苯基) 烟酰胺 (43) 的合成

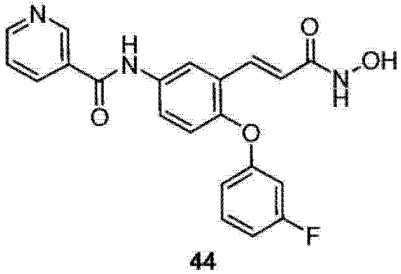
[0390] 如实施例 28 中所述合成标题化合物。EM(计算) :409.08 ;MS(M+1H) = 410.5。



43

实施例 32 :(E)-N-(4-(3- 氟苯氧基)-3-(3-(羟基氨基)-3- 氧代丙 -1- 烯基) 苯基) 烟酰胺 (44) 的合成

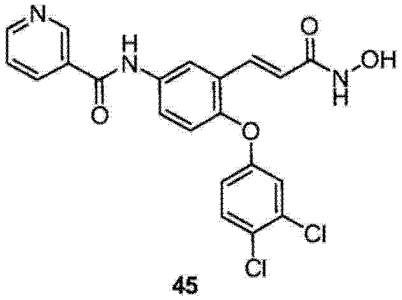
[0391] 如实施例 28 中所述合成标题化合物。EM(计算) :393.11 ;MS(M+1H) = 394.0。



44

实施例 33 :(E)-N-(4-(3,4- 二氯苯氧基)-3-(3-(羟基氨基)-3- 氧代丙 -1- 烯基) 苯基) 烟酰胺 (45) 的合成

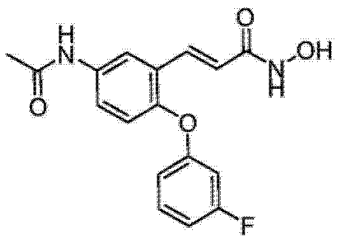
[0392] 如实施例 28 中所述合成标题化合物。EM(计算) :443.04 ;MS(M+1H) = 444.5。



45

实施例 34 :(E)-3-(5- 乙酰氨基 -2-(3- 氟苯氧基) 苯基)-N- 羟基丙烯酰胺 (46) 的合成

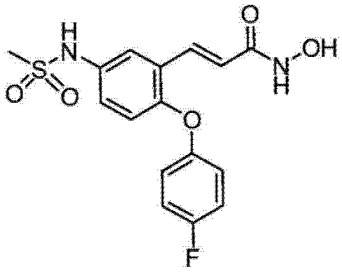
[0393] 如实施例 28 中所述合成标题化合物。EM(计算) :330.10 ;MS(M+1H) = 331.0。



46

实施例 35 :(E)-3-(2-(4- 氟苯氧基)-5-(甲基磺酰胺基) 苯基)-N- 羟基丙烯酰胺 (47) 的合成

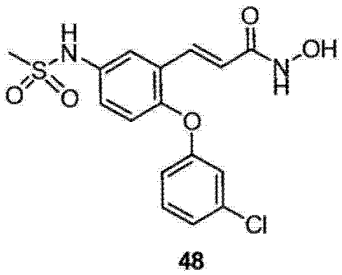
[0394] 如实施例 28 中所述合成标题化合物。EM(计算) :366.07 ;MS(M+1H) = 367.0。



47

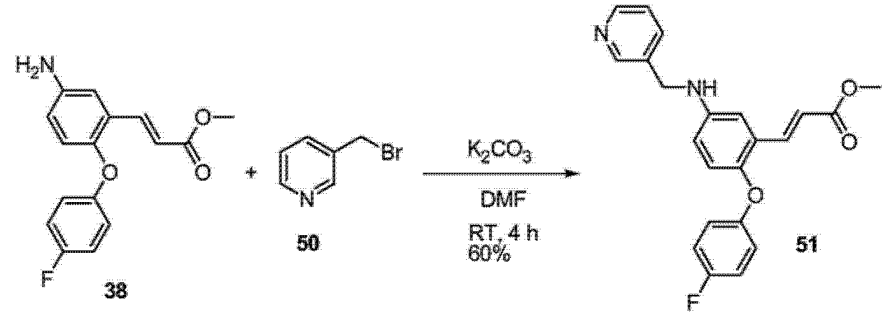
实施例 36 :(E)-3-(2-(3- 氯苯氧基)-5-(甲基磺酰胺基) 苯基)-N- 羟基丙烯酰胺 (48) 的合成

[0395] 如实施例 28 中所述合成标题化合物。EM(计算) :382.04 ;MS(M+1H) = 383.0。

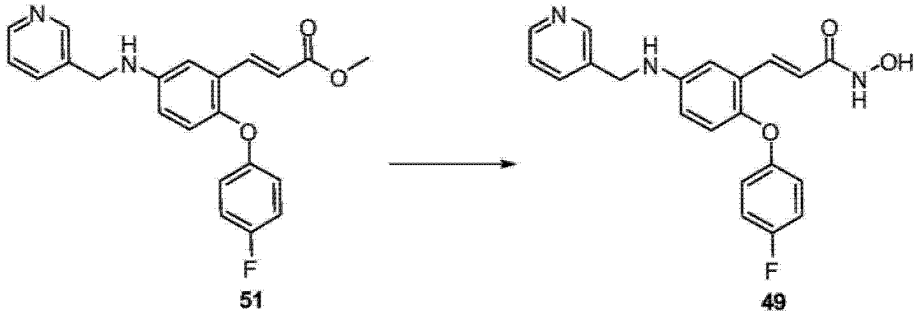


48

实施例 37 :(E)-3-(2-(4- 氟苯氧基)-5-(吡啶 -3- 基甲基氨基) 苯基)-N- 羟基丙烯酰胺的合成 (49)



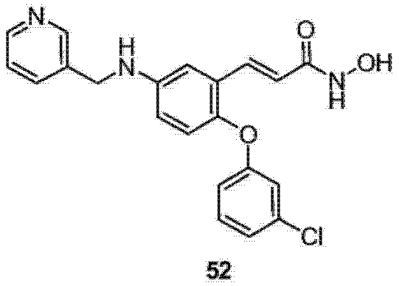
[0396] 步骤 1：向 3-[2-(4- 氟 - 苯氧基)-5- 氨基 - 苯基]- 丙烯酸甲酯 (38)(72mg, 0.22mmol) 和 3- 溴甲基 - 吡啶 (50)(41mg,0.24mmol) 的混合物中加入 3mL DMF 和 200mg K_2CO_3 并在室温下搅拌 4h。反应完成后，减压浓缩该混合物，并且用乙酸乙酯 (75mL) 对残余物进行处理。该乙酸乙酯溶液用酸 (HCl) 和碱 ($NaHCO_3$) 和盐水 (10mL x2) 洗涤，经无水 $MgSO_4$ 干燥，过滤，并蒸发至干。该残余物经 SiO_2 柱塞 (用己烷中的 33％至 50％ EtOAc 洗脱) 纯化，得到呈粘稠的油的 (E)-3-(2-(4- 氟苯氧基)-5-(吡啶 -3- 基甲基氨基) 苯基) 丙烯酸甲酯 (51)(46mg,0.12mmol,61％)。ESI MS m/z379.4 $(M+H)^+$。



[0397] 步骤 2：按照实施例 28 步骤 5 中描述的相同程序，由 3-{2-(4- 氟 - 苯氧基)-5-[(吡啶 -3- 基甲基)- 氨基]- 苯基 }- 丙烯酸甲酯 (51)(84mg,0.22mmol) 制备该化合物，经 HPLC 纯化后得到呈白色固体的 43mg(0.10mmol,47％)(E)-3-(2-(4- 氟苯氧基)-5-(吡啶 -3- 基甲基氨基) 苯基)-N- 羟基丙烯酰胺 (49)。EM(计算):379.13 ;ESI MS m/z380.1 $(M+H)^+$。

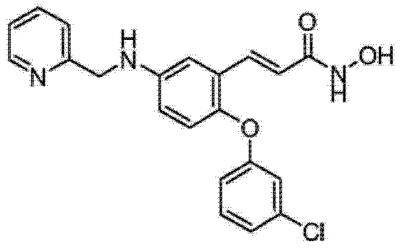
实施例 38：(E)-3-(2-(3- 氯苯氧基)-5-(吡啶 -3- 基甲基氨基) 苯基)-N- 羟基丙烯酰胺 (52) 的合成

[0398] 如实施例 37 中所述合成标题化合物。EM(计算):395.1 ;MS(M+1H) ＝ 396.1。



实施例 39：(E)-3-(2-(3- 氯苯氧基)-5-(吡啶 -2- 基甲基氨基) 苯基)-N- 羟基丙烯酰胺 (53) 的合成

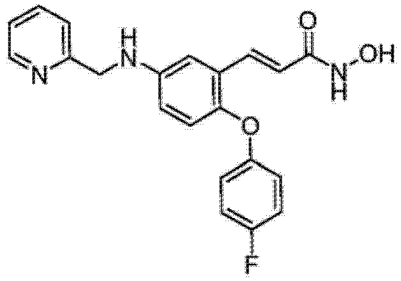
[0399] 如实施例 37 中所述合成标题化合物。EM(计算):395.1 ;MS(M+1H) ＝ 396.0。



53

实施例 40 :(E)-3-(2-(4- 氟苯氧基)-5-(吡啶 -2- 基甲基氨基) 苯基)-N- 羟基丙烯酰胺 (54) 的合成

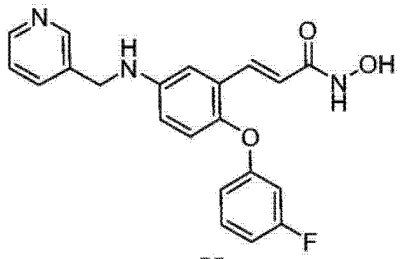
[0400] 如实施例 37 中所述合成标题化合物。EM(计算) :379.13 ;MS(M+1H) ＝ 380.5。



54

实施例 41 :(E)-3-(2-(3- 氟苯氧基)-5-(吡啶 -3- 基甲基氨基) 苯基)-N- 羟基丙烯酰胺 (55) 的合成

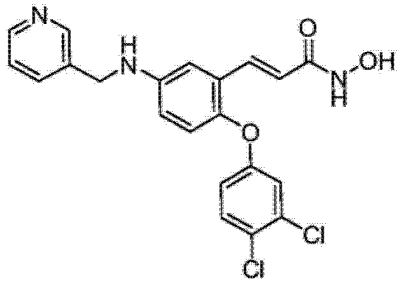
[0401] 如实施例 37 中所述合成标题化合物。EM(计算) :379.13 ;MS(M+1H) ＝ 380.0。



55

实施例 :(E)-3-(2-(3,4- 二氯苯氧基)-5-(吡啶 -3- 基甲基氨基) 苯基)-N- 羟基丙烯酰胺 (56) 的合成

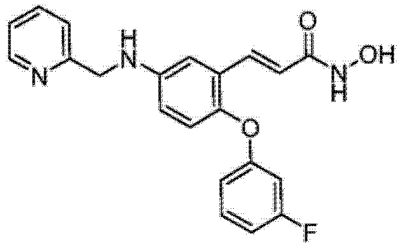
[0402] 如实施例 37 中所述合成标题化合物。EM(计算) :429.06 ;MS(M+1H) ＝ 430.5。



56

实施例 43 :(E)-3-(2-(3- 氟苯氧基)-5-(吡啶 -2- 基甲基氨基) 苯基)-N- 羟基丙烯酰胺 (57) 的合成

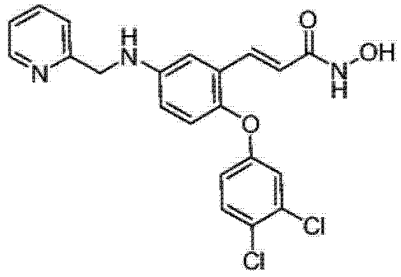
[0403] 如实施例 37 中所述合成标题化合物。EM(计算) :379.13 ;MS(M+1H) ＝ 380.5。



57

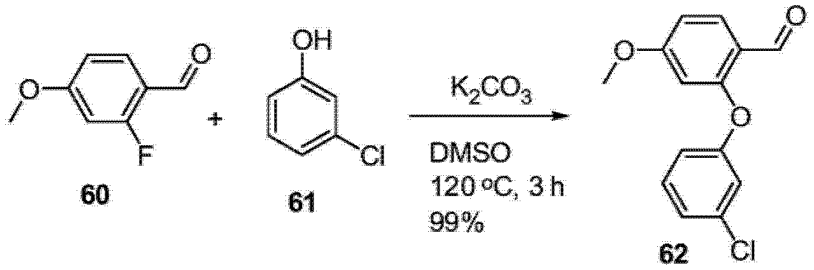
实施例 44 :(E)-3-(2-(3,4- 二氯苯氧基)-5-(吡啶 -2- 基甲基氨基) 苯基)-N- 羟基丙烯酰胺 (58) 的合成

[0404] 如实施例 37 中所述合成标题化合物。EM(计算) :429.06 ;MS(M+1H) = 430.0。

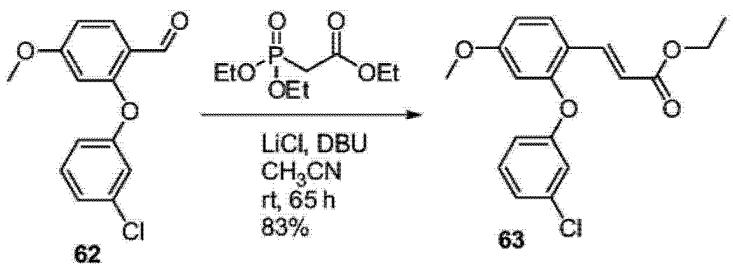


58

实施例 45 :(E)-3-(2-(3- 氯苯氧基)-4-(吡啶 -3- 基甲氧基) 苯基)-N- 羟基丙烯酰胺 (59) 的合成

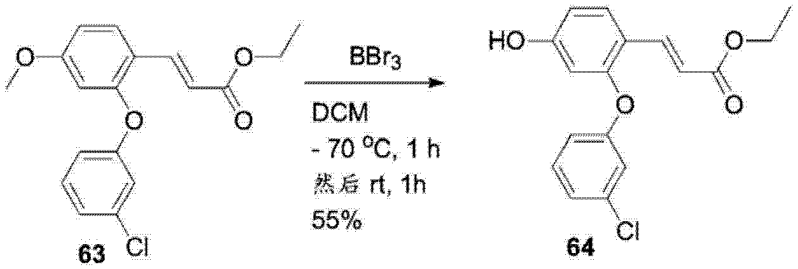


[0405] 步骤 1 :在室温下,向 2- 氟 -4- 甲氧基 - 苯甲醛 (60)(616mg,4.0mmol) 和 3- 氯苯酚 (61)(617mg,4.8mmol) 在 DMSO(5mL) 中的溶液中加入 K_2CO_3(1.10g,8.0mmol)。所得混合物用 N_2 吹洗,并在密封容器中在 120℃下搅拌加热 3h。该反应混合物冷却至室温并倒入盐水中后,该混合物用乙酸乙酯 (35mL x3) 萃取。合并的萃取物用盐水 (10mL x2) 洗涤,经无水 $MgSO_4$ 干燥,过滤,并蒸发至干。残余物经 SiO_2 柱塞 (用己烷中的 15% EtOAc 洗脱) 纯化,得到呈粘稠的油的 2-(3- 氯苯氧基)-4- 甲氧基苯甲醛 (62)(1.05g,4.0mmol,99%)。ESI MS m/z263.1$(M+H)^+$。

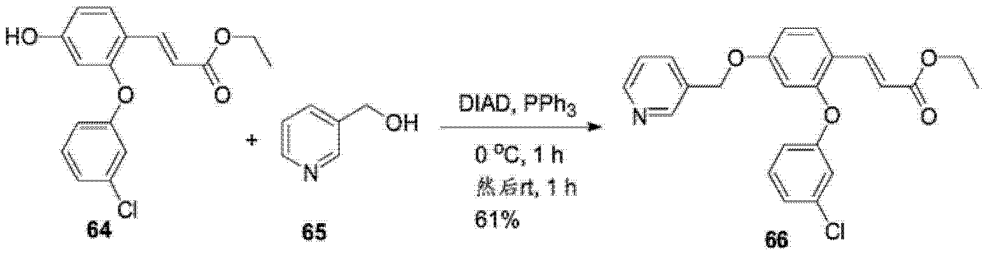


[0406] 步骤 2 :在室温下,向 2-(3- 氯 - 苯氧基)-4- 甲氧基 - 苯甲醛 (62)(469mg,1.79mmol) 和膦酰基乙酸三乙酯 (803mg,3.58mmol) 在乙腈 (20mL) 中的搅拌溶液中加入

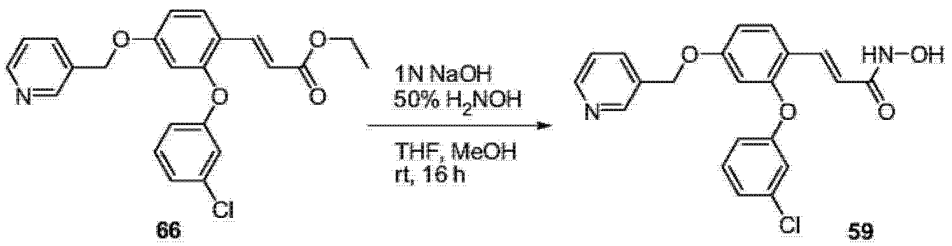
LiCl(228mg,5.36mmol),随后加入 DBU(0.802mL,5.36mmol)。所得混合物在室温下搅拌 65h。减压浓缩反应混合物后,残余物用乙酸乙酯 (100mL) 处理。EtOAc 溶液用 1M HCl 水溶液 (10mL x2)、饱和 $NaHCO_3$ 水溶液 (10mL) 和盐水 (10mL) 洗涤,经无水 $MgSO_4$ 干燥,过滤,并蒸发至干。残余物经 SiO_2 柱塞 (用己烷中的 10% 至 25% EtOAc 洗脱) 纯化,得到呈粘稠的油的 (E)-3-(2-(3- 氯苯氧基)-4- 甲氧基苯基) 丙烯酸乙酯 (63)(498mg,1.50mmol,83%)。ESI MS m/z333.3(M+H)$^+$。



[0407] 步骤 3 :在 -70℃和 N_2 下,向 3-[2-(3- 氯 - 苯氧基)-4- 甲氧基 - 苯基]- 丙烯酸乙酯 (63)(498mg,1.50mmol) 在 DCM(10mL) 中的搅拌溶液中加入 1M BBr_3 的 DCM 溶液 (4.5mL,4.5mmol)。在 -70℃下搅拌所得混合物 1h,然后使之升温至室温。该反应混合物在室温下再搅拌一小时后,通过在 0℃下缓慢加入饱和 $NaHCO_3$ 水溶液 (10mL) 猝灭反应。将该混合物转移至分液漏斗中并分离有机层。水层用 DCM(30mL x3) 进一步萃取。合并的有机相用盐水 (10mL x2) 洗涤,经无水 $MgSO_4$ 干燥,过滤,并蒸发至干。残余物经 SiO_2 柱塞 (用己烷中的 10% 至 25% EtOAc 洗脱) 纯化,得到呈灰白色粉末的 (E)-3-(2-(3- 氯苯氧基)-4- 羟基苯基) 丙烯酸乙酯 (64)(267mg,0.84mmol,56%)。ESI MS m/z318.9(M+H)$^+$。



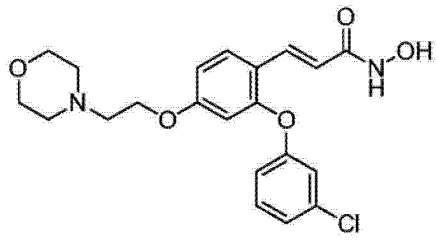
[0408] 步骤 4 :在 0℃和 N_2 下,向 3-[2-(3- 氯 - 苯氧基)-4- 羟基 - 苯基]- 丙烯酸乙酯 (64)(64mg,0.20mmol) 和 3- 吡啶甲醇 (65)(35mg,0.32mmol) 在 THF(2mL) 中的搅拌溶液中加入 Ph_3P(79mg,0.30mmol),随后加入 DIAD(0.063mL,0.32mmol) 的 THF(1mL) 溶液。所得混合物在 0℃下搅拌 1h,然后在室温下搅拌 16h。减压浓缩反应混合物后,残余物用乙酸乙酯 (75mL) 处理。该溶液用盐水 (10mL x2) 洗涤,经无水 $MgSO_4$ 干燥,过滤,并蒸发至干。残余物经 SiO_2 柱塞 (用己烷中的 33% 至 50% EtOAc 洗脱) 纯化,得到呈粘稠的油的 (E)-3-(2-(3- 氯苯氧基)-4-(吡啶 -3- 基甲氧基) 苯基) 丙烯酸乙酯 (66)(50mg,0.12mmol,61%)。ESI MS m/z410.2(M+H)$^+$。



[0409] 步骤 5 :在室温下,向 3-[2-(3- 氯 - 苯氧基)-4-(吡啶 -3- 基甲氧基)- 苯基]- 丙烯酸乙酯 (66)(91mg,0.22mmol) 在 THF(1.2mL) 和 MeOH(1.2mL) 中的搅拌溶液中加入 50% NH_2OH 水溶液 (0.73mL,11mmol) 和 1N NaOH 水溶液 (0.5mL,0.5mmol)。所得混合物在室温下搅拌 16h。减压浓缩反应混合物后,得到的水性悬浮液用 DMSO(1.5mL) 稀释,并经 HPLC 纯化,得到呈白色固体的 (E)-3-(2-(3- 氯苯氧基)-4-(吡啶 -3- 基甲氧基) 苯基)-N- 羟基丙烯酰胺 (59)(54mg,0.14mmol,62%)。EM(计算) :396.09 ;ESI MS m/z397.5(M+H)$^+$。

实施例 46 :(E)-3-(2-(3- 氯苯氧基)-4-(2- 吗啉基乙氧基) 苯基)-N- 羟基丙烯酰胺 (67) 的合成

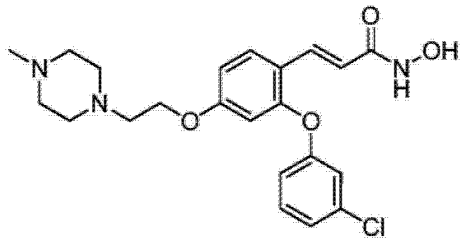
[0410] 如实施例 45 中所述合成标题化合物。EM(计算) :418.13 ;MS(M+1H) = 419.5。



67

实施例 47 :(E)-3-(2-(3- 氯苯氧基)-4-(2-(4- 甲基哌嗪 -1- 基) 乙氧基) 苯基)-N- 羟基丙烯酰胺 (68) 的合成

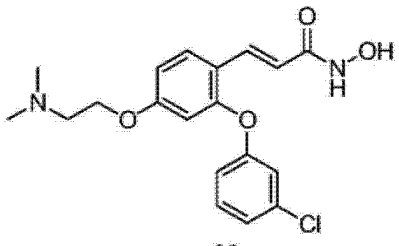
[0411] 如实施例 45 中所述合成标题化合物。EM(计算) :431.16 ;MS(M+1H) = 432.5。



68

实施例 48 :(E)-3-(2-(3- 氯苯氧基)-4-(2-(二甲基氨基) 乙氧基) 苯基)-N- 羟基丙烯酰胺 (69) 的合成

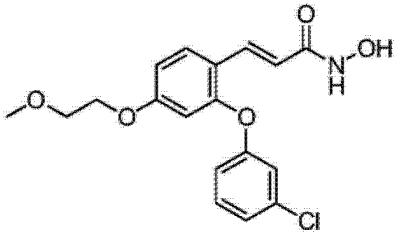
[0412] 如实施例 45 中所述合成标题化合物。EM(计算) :376.12 ;MS(M+1H) = 377.5。



69

实施例 49 :(E)-3-(2-(3- 氯苯氧基)-4-(2- 甲氧基乙氧基) 苯基)-N- 羟基丙烯酰胺 (70) 的合成

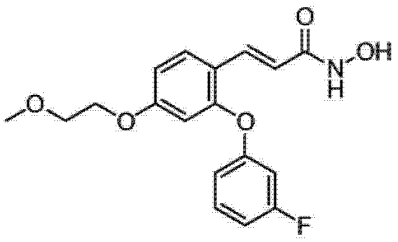
[0413] 如实施例 45 中所述合成标题化合物。EM(计算) :363.09 ;MS(M+1H) = 364.5。



70

实施例 50 :(E)-3-(2-(3- 氟苯氧基)-4-(2- 甲氧基乙氧基) 苯基)-N- 羟基丙烯酰胺 (71) 的合成

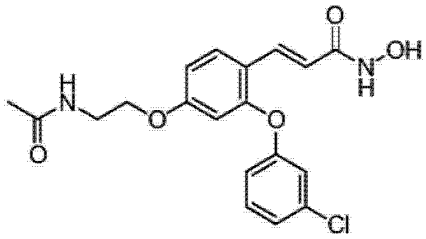
[0414] 如实施例 45 中所述合成标题化合物。EM(计算) :347.12 ;MS(M+1H) = 348.0。



71

实施例 51 :(E)-3-(4-(2- 乙酰氨基乙氧基)-2-(3- 氯苯氧基) 苯基)-N- 羟基丙烯酰胺 (72) 的合成

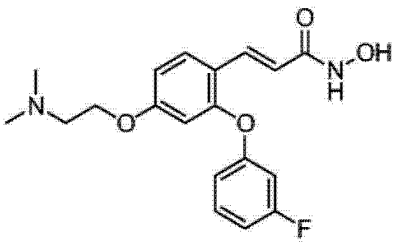
[0415] 如实施例 45 中所述合成标题化合物。EM(计算) :390.09 ;MS(M+1H) = 391.5。



72

实施例 52 :(E)-3-(2-(3- 氟苯氧基)-4-(2-(二甲基氨基) 乙氧基) 苯基)-N- 羟基丙烯酰胺 (73) 的合成

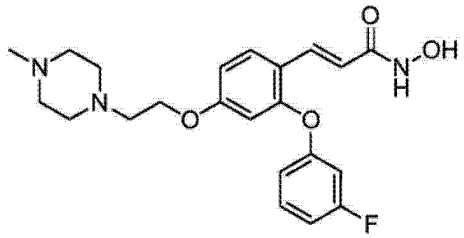
[0416] 如实施例 45 中所述合成标题化合物。EM(计算) :360.14 ;MS(M+1H) = 361.0。



73

实施例 53 :(E)-3-(2-(3- 氟苯氧基)-4-(2-(4- 甲基哌嗪 -1- 基) 乙氧基) 苯基)-N- 羟基丙烯酰胺 (74) 的合成

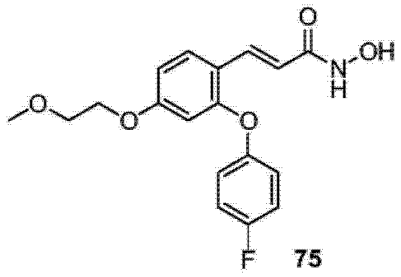
[0417] 如实施例 45 中所述合成标题化合物。EM(计算) :415.19 ;MS(M+1H) = 416.5。



74

实施例 54 :(E)-3-(2-(4- 氟苯氧基)-4-(2- 甲氧基乙氧基) 苯基)-N- 羟基丙烯酰胺 (75) 的合成

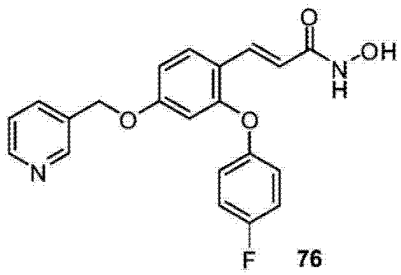
[0418] 如实施例 45 中所述合成标题化合物。EM(计算) :347.12 ;MS(M+1H) = 348.0。



75

实施例 55 :(E)-3-(2-(4- 氟苯氧基)-4-(吡啶 -3- 基甲氧基) 苯基)-N- 羟基丙烯酰胺 (76) 的合成

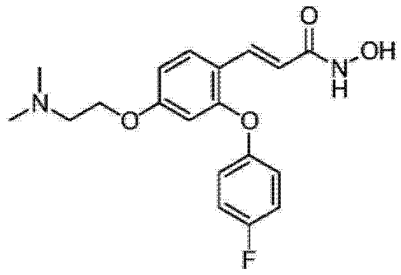
[0419] 如实施例 45 中所述合成标题化合物。EM(计算) :380.11 ;MS(M+1H) = 381.5。



76

实施例 56 :(E)-3-(2-(4- 氟苯氧基)-4-(2-(二甲基氨基) 乙氧基) 苯基)-N- 羟基丙烯酰胺 (77) 的合成

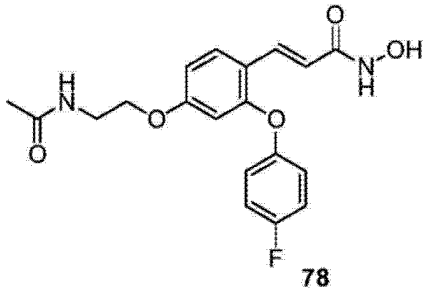
[0420] 如实施例 45 中所述合成标题化合物。EM(计算) :360.14 ;MS(M+1H) = 361.5。



77

实施例 57 :(E)-3-(4-(2- 乙酰氨基乙氧基)-2-(4- 氟苯氧基) 苯基)-N- 羟基丙烯酰胺 (78) 的合成

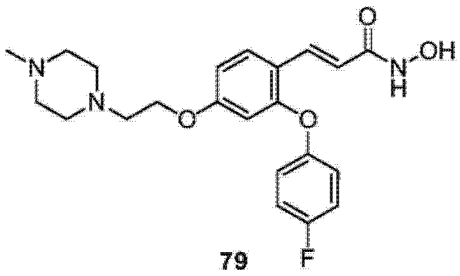
[0421] 如实施例 45 中所述合成标题化合物。EM(计算) :374.12 ;MS(M+1H) = 375.0。



78

实施例 58 :(E)-3-(2-(4- 氟苯氧基)-4-(2-(4- 甲基哌嗪 -1- 基) 乙氧基) 苯基)-N- 羟基丙烯酰胺 (79) 的合成

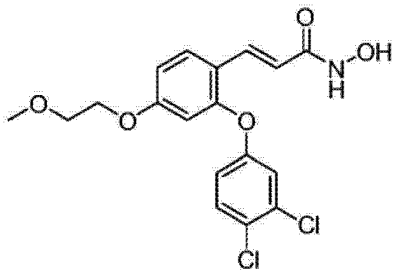
[0422] 如实施例 45 中所述合成标题化合物。EM(计算) :415.19 ;MS(M+1H) = 416.5。



79

实施例 59 :(E)-3-(2-(3,4- 二氯苯氧基)-4-(2- 甲氧基乙氧基) 苯基)-N- 羟基丙烯酰胺 (80) 的合成

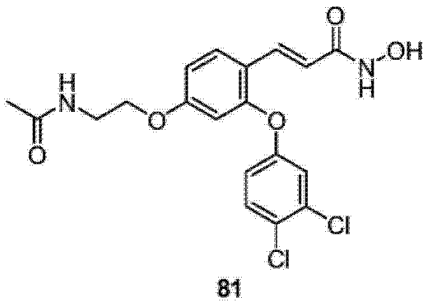
[0423] 如实施例 45 中所述合成标题化合物。EM(计算) :397.04 ;MS(M+1H) = 398.0。



80

实施例 60 :(E)-3-(4-(2- 乙酰氨基乙氧基)-2-(3,4- 二氯苯氧基) 苯基)-N- 羟基丙烯酰胺 (81) 的合成

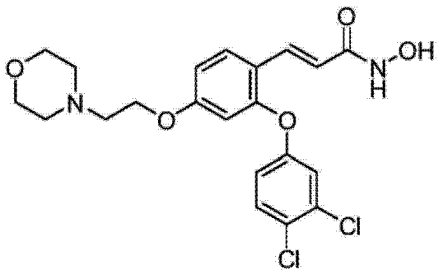
[0424] 如实施例 45 中所述合成标题化合物。EM(计算) :424.05 ;MS(M+1H) = 425.0。



81

实施例 61 :(E)-3-(2-(3,4- 二氯苯氧基)-4-(2- 吗啉基乙氧基) 苯基)-N- 羟基丙烯酰胺 (82) 的合成

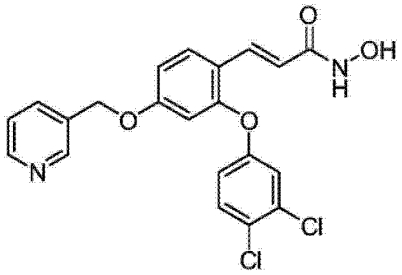
[0425] 如实施例 45 中所述合成标题化合物。EM(计算) :452.09 ;MS(M+1H) = 453.0。



82

实施例 62 :(E)-3-(2-(3,4- 二氯苯氧基)-4-(吡啶 -3- 基甲氧基) 苯基)-N- 羟基丙烯酰胺 (83) 的合成

[0426] 如实施例 45 中所述合成标题化合物。EM(计算) :430.04 ;MS(M+1H) = 431.5。



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生物学实施例

细胞系和试剂

[0427] 细胞系从 DSMZ(Braunschweig, Germany) 或 ATCC(Manassas, VA) 获得。细胞在含有 10%胎牛血清的 RPMI 1640 中,在 5% CO_2/ 空气培养箱中于 37℃生长。毒胡萝卜内酯和 BAPTA-AM 来自 Calbiochem(San Diego,CA)。3-((二甲基氨基) 甲基)-N-(2-(4-(羟基氨基甲酰基) 苯氧基) 乙基) 苯并呋喃 -2- 甲酰胺是如先前所述合成的广谱 HDAC 抑制剂。对 HDAC 同种型具有不同程度的特异性的其他类似物如本文所述合成。

实施例 63 :组蛋白脱乙酰酶活性

[0428] HDAC 活性使用连续胰蛋白酶偶联试验进行测量,该试验先前已进行了详细描述 (US 20070281934 ;Schultz 等,Biochemistry,43(34),11083-11091,2004 ;Kim 等,(2006), Methods MolBiol.,325 :273-283)。对于抑制剂的表征,在荧光读板仪中使用 96- 孔测定板在 100μL 反应体积中进行测量。对每种同工酶,在补充有 0-0.05%浓度的牛血清白蛋白的反应缓冲液 (50mM HEPES,100mM KCl,0.001%吐温 -20,5% DMSO, pH 7.4) 中的 HDAC 蛋白质与不同浓度的抑制剂混合,并温育 15 分钟。加入胰蛋白酶至 50nM 的最终浓度,并加入乙酰基 -Gly-Ala-(N- 乙酰基 -Lys)-AMC 至 25-100μM 的最终浓度以引发反应。30 分钟滞后时间后,使用 355nm 激发波长和 460nm 检测波长在 30 分钟的时间范围内测量荧光。荧光随时间的增加用作反应速度的量度。使用程序 BatchKi(Biokin, Pullman, WA) 得到抑制常数 K_i(app)。结果总结于以下表 B 中。

表 B :代表性 HDAC8- 选择性抑制剂的 HDAC IC_{50} 值的比较

化合物号	HDAC1 IC_{50}(μM)	HDAC8 IC_{50}(μM)	HDAC6 IC_{50}(μM)
6	C	A	C

7	C	A	B
8	C	A	B
9	C	A	C
10	C	A	B
11	C	A	B
12	C	A	C
13	C	A	C
14	C	A	C
15	C	A	B
16	C	A	C
17	D	A	D
20	C	A	C
42	D	A	D
49	D	A	C
59	C	A	B
67	C	A	B
68	C	A	B
69	B	A	B
80	D	A	C

A ＝小于或等于 0.1uM

B ＝大于 0.1μM 但小于或等于 1μM

C ＝大于 1μM 但小于或等于 10μM

D ＝大于 10uM

实施例 64：细胞增殖试验

[0429] 肿瘤细胞系和人脐静脉内皮细胞 (HUVEC) 培养至少两个倍增时间，并在化合物暴露结束时使用制造商推荐的阿拉玛蓝 ™(Alamar Blue™)(Biosource，Camarillo，CA) 荧光细胞增殖试验监测其生长。化合物在 96- 孔板中的三份相同的孔中测定。以 50％ (GI_{50}) 和

95％置信区间抑制细胞生长所需的浓度通过使用 4- 参数逻辑方程经非线性回归估算。测量了 HDAC8 选择性抑制剂化合物对 Jurkat 细胞的细胞增殖的影响。细胞凋亡通过膜联蛋白 -V 流式细胞术测量。生长抑制通过阿拉玛蓝试验测量。通过阿拉玛蓝试验测量的 Jurkat 细胞的生长抑制在表 C 中显示。细胞用化合物处理 3 天。

表 C :通过阿拉玛蓝试验测量的 Jurkat 细胞的生长抑制

化合物	GI_{50} (μM)
6	1.43
7	--
8	6.1
9	2.00
10	2.25
11	1.98
12	1.80
13	2.5
14	3.58
15	3.37
16	>20
17	--
20	9.70

实施例 65 :Western 印迹分析

[0430] 细胞经 PBS 洗涤，并重悬于三去污剂裂解缓冲液 [50mM Tris-Cl(pH 8.0)，150mM NaCl，0.1％ SDS，0.5％脱氧胆酸，1.0％ NP-40，补充有 1mM EDTA，1mM PMSF，1mM Na_3VO_4，2mM β- 甘油磷酸盐和全蛋白酶抑制剂混合物 (Roche Molecular Biochemicals，Indianapolis，IN)] 中，在冰上保持 10 分钟。离心分离后，等量的蛋白质在 SDS- 聚丙烯酰胺凝胶 (Bio-Rad Laboratories，Hercules，CA) 上进行分析。使用半干转移单元 (Semi-dry Transfer Cell)(Bio-Rad Laboratories，Hercules，CA) 将凝胶转移至聚偏二氟乙烯膜，并使用抗 -Hsc70 抗体进行 Western 印迹，以控制加载和转移。使用 Odyssey 红外成像系统 (LICOR，Lincoln，NE) 对条带进行成像，并在线性范围内进行定量并对 Hsc70 进行标准化。

实施例 66 :细胞凋亡试验

[0431] 在单独用抑制剂处理以及与 qVD、BAPTA-AM、毒胡萝卜内酯和磷脂酶 C 抑制剂联合处理 2 或 3 天后，使用膜联蛋白 -V 染色评估细胞毒性。按照制造商的方案，用 FACSCalibur 仪器 (Becton-Dickinson，San Jose，CA) 使用来自 BioVision(Mountain View，CA) 的试剂测定膜联蛋白 -V 结合。

实施例 67 :胱天蛋白酶激活试验

[0432] 在用抑制剂处理后，按照制造商的方案，使用 Apotarget 胱天蛋白酶比色蛋白酶试验 (BioSource International，Camarillo，CA) 在 Jurkat 细胞中测量胱天蛋白酶的酶活性。

实施例 68 :细胞内钙的测量

[0433] 对于荧光光度法测量，细胞 ($1X10^6$ 个细胞 /mL) 在含有 10％胎牛血清和 5μM

Indo1-AM(Invitrogen) 的 Hanks 平衡盐溶液中 (HBSS ;Invitrogen) 中在 37℃下黑暗中培养 1h。然后收获细胞,离心 (200Xg 进行 5min),并用 HBSS 洗涤三次以除去细胞外 Indo1,并在 HBSS 中重调至 $1X10^6$ 个细胞 /mL。在 37℃下,用荧光读板仪 (Fluoroskan Ascent FL ; Thermo Scientific) 在各个实验的整个过程中监测荧光。5min 温度平衡期后,在一分钟期间内以 6 秒钟的间隔,将样品在 338nm 下激发并且在 405nm 和 485nm 下收集发射,分别对应于 Ca^{2+} 结合的和不含 Ca^{2+} 的 Indo1 的发射荧光。随后加入药物 (或对照),并继续获取 5 分钟。在测量结束时通过加入 10μM 离子霉素来确定最大比值。细胞内 $[Ca^{2+}]$ 变化显示为 Ca^{2+} 结合的和不含 Ca^{2+} 的 Indo1 比值的变化。实施例 69 :HDAC 抑制剂化合物的药代动力学分析

[0434] 使用测试化合物在雄性大鼠中进行的该研究被设计为提供关于其药代动力学的初步信息。测试化合物通过口饲联合施用。

[0435] 该研究中使用的大鼠的规格如下 :

品系 :CD® IGS 大鼠 (起源于 Sprague-Dawley)

来源 :Charles River 实验室

针对口服给药的手术改良 :一个门静脉插管和一个颈静脉插管给药时的体重范围为 350g 至 375g

[0436] 在给药前,使大鼠在实验室条件下适应至少 24 小时。给药前夜,阻止大鼠进食,并在 3 小时采血时间点后立即恢复进食。随意提供水。大鼠单独关在半透明的聚碳酸酯笼中。

[0437] 将测试化合物制备成 3.0mg/ml 溶液 (1% MC/0.4% Cr EL,在 WFI 中)。

[0438] 大鼠通过口饲联合施用一个剂量的测试化合物。剂量体积根据在临给药前收集的体重数据进行调整。

[0439] 剂量体积为 1ml/kg,而标称剂量为 3mg/kg。

[0440] 在给药后 5 分钟、20 分钟、1 小时、3 小时、6 小时、9 小时和 24 小时从口服给药的大鼠中采集血液样品。样品采集至含有抗凝剂 (肝素锂) 的血浆分离器 Microtainer 管中。经离心 (在 5000xg 下 5min) 制备血浆样品,将至少 100μL 转移至存储管中,并在干冰上冷冻。在准备用于分析前,样品一直保持在约 -75℃下。

[0441] 将血浆样品解冻并将 75μL 等分试样转移至离心管中,其中加入 10μL 内标溶液 (0.5μg/mL) 的等分试样。在进一步处理前,该样品不用空白血浆稀释。通过加入 300μL 甲醇,随后离心 (在 16,000xg 下 20min) 来沉淀可溶性蛋白质。使样品蒸发至干,并在 100μL 含有 0.2% 甲酸和 10% 甲醇的水中重建。所有样品都加载到维持在 6℃的自动进样器中,并使用 LC-MS/MS 评估测试化合物的浓度。使用计算机程序 WinNonlin(Professional Edition, Pharsight Corporation,5.01 版) 估算血浆浓度数据。该分析是使用标称采样时间和采用均匀加权的非房室法而完成的。药代动力学参数的估计值包括终末半衰期、稳态分布体积以及在浓度 - 时间曲线下面积 (AUC)。

[0442] 将 HDAC 抑制剂 3-((二甲基氨基) 甲基)-N-(2-(4-(羟基氨基甲酰基) 苯氧基) 乙基) 苯并呋喃 -2- 甲酰胺加入至盒中以作为标准,因为该化合物的药代动力学先前已在大鼠中确定。

实施例 70a :肠胃外组合物

[0443] 为了制备适合通过注射给药的肠胃外药物组合物,将 100mg 本文所述的选择性

HDAC8 抑制剂化合物的水溶性盐溶解在 DMSO 中，然后与 10mL0.9％无菌盐水混合。将混合物加入到适合通过注射给药的剂量单位形式中。

[0444] 在另一个实施方案中，将下列成分混合以形成可注射制剂。

成分	量
本文所述的选择性 HDAC8 抑制剂化合物	1.2 g
乙酸钠缓冲溶液(0.4 M)	2.0 mL
HCl (1 N)或 NaOH(1 M)	适量，至合适的 pH
水(蒸馏的，无菌的)	适量，至 20 mL

[0445] 将除水以外的以上所有成分混合，并在搅拌下加热至 60-70℃。然后在剧烈搅拌下加入 60℃的足量的水，以使所述成分乳化，然后加适量的水至 100g。

实施例 70b：口服组合物

[0446] 为了制备用于口服递送的药物组合物，将 100mg 本文所述的选择性 HDAC8 抑制剂化合物与 750mg 淀粉混合。将混合物加入到适合口服给药的口服剂量单位如硬明胶胶囊中。

[0447] 在另一个实施方案中，将下列成分紧密地混合并压制成单一刻痕片剂。

成分	每片中的量，mg
本文所述的选择性 HDAC8 抑制剂化合物	400
玉米淀粉	50
交联羧甲基纤维素钠	25
乳糖	120
硬脂酸镁	5

[0448] 在又一实施方案中，将下列成分紧密地混合并装入硬壳明胶胶囊中。

成分	每片中的量，mg
本文所述的选择性 HDAC8 抑制剂化合物	200
乳糖，喷雾干燥的	148
硬脂酸镁	2

[0449] 在又一实施方案中，将下列成分混合以形成用于口服给药的悬浮液。

成分	量
本文所述的选择性 HDAC8 抑制剂化合物	1.0 g
富马酸	0.5 g
氯化钠	2.0 g
对羟基苯甲酸甲酯	0.15 g
对羟基苯甲酸丙酯	0.05 g
砂糖	25.5 g
山梨醇(70%溶液)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
调味剂	0.035 mL
着色剂	0.5 mg
蒸馏水	适量，至 100 mL

实施例 70c :舌下（硬锭剂）组合物

[0450] 为了制备用于颊部递送的药物组合物，例如硬锭剂，将 100mg 本文所述的选择性 HDAC8 抑制剂化合物与 420mg 糖粉混合，该糖粉已混合有 1.6mL 低度玉米糖浆、2.4mL 蒸馏水和 0.42mL 薄荷提取物。将混合物轻柔地共混，并倒入模具中，以形成适合颊部给药的锭剂。

实施例 70d :吸入组合物

[0451] 为了制备用于吸入递送的药物组合物，将 20mg 本文所述的选择性 HDAC8 抑制剂化合物与 50mg 无水柠檬酸和 100mL0.9％氯化钠溶液混合。将混合物加入到适合吸入给药的吸入递送单元如喷雾器中。

实施例 70e :直肠凝胶组合物

[0452] 为了制备用于直肠递送的药物组合物，将 100mg 本文所述的选择性 HDAC8 抑制剂化合物与 2.5g 甲基纤维素 (1500mPa)、100mg 对羟基苯甲酸甲酯、5g 甘油和 100mL 纯净水混合。然后将得到的凝胶混合物加入到适合直肠给药的直肠递送单元如注射器中。

实施例 70f :栓剂制剂

[0453] 通过将本文所述的选择性 HDAC8 抑制剂化合物与 Witepsol™H-15（饱和植物脂肪酸的甘油三酯 ;Riches-Nelson,Inc.,New York）混合制备总重量为 2.5g 的栓剂，该栓剂具有下列组成。

成分	每个栓剂中的量(mg)
本文所述的选择性 HDAC8 抑制剂化合物	500
Witepsol® H-15	余量

实施例 70g :局部凝胶组合物

[0454] 为了制备局部凝胶药物组合物，将 100mg 本文所述的选择性 HDAC8 抑制剂化合物

与1.75g羟丙基纤维素、10mL丙二醇、10mL肉豆蔻酸异丙酯和100mL纯化的醇USP混合。然后将得到的凝胶混合物加入到适合局部给药的容器如管中。

实施例70h:眼用溶液组合物

[0455] 为了制备眼用溶液药物组合物,将100mg本文所述的选择性HDAC8抑制剂化合物与0.9g NaCl在100mL纯净水中混合,并使用0.2微米滤器过滤。然后将得到的等渗溶液加入到适合眼部给药的眼部递送单元如滴眼液容器中。

[0456] 本文所述的实施例和实施方案仅用于说明的目的,并且各种修改和变化将包括在所附权利要求书的公开内容和范围的精神和范围内。

Abstract

Described herein are compounds and pharmaceutical compositions containing such compounds, which inhibit the activy of histone deacetylase 8 (HDAC8). Also described herein are methods of using such HDAC8 inhibitors, alone and in combination with other compounds, for treating diseases or conditions that would benefit from inhibition of HDAC8 activity.