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[57]	Abstract:	The present invention provides for compounds of formula (I) wherein A1, A2, A3, A4, X1, X2, Y1, L1, G1, Rx, and Ry have any of the values defined thereof in the specification, and pharmaceutically acceptable salts thereof, that are useful as agents in the treatment of diseases and conditions, including inflammatory diseases, cancer, and AIDS. Also provided are pharmaceutical compositions comprising one or more compounds of formula (I).		

$-OC(O)NR^jR^k$, $-SR^h$, $-S(O)_2R^h$, $-S(O)_2NR^jR^k$, $-C(O)R^h$, $-C(O)OR^h$, $-C(O)NR^jR^k$, $-NR^jR^k$, $-N(R^h)C(O)R^i$, $-N(R^h)S(O)_2R^i$, $-N(R^h)C(O)O(R^i)$, $-N(R^h)C(O)NR^jR^k$, $-(C_1\text{-}C_6$ alkylenyl)-OR^h, $-(C_1\text{-}C_6$ alkylenyl)-$OC(O)R^i$, $-(C_1\text{-}C_6$ alkylenyl)-$OC(O)NR^jR^k$, $-(C_1\text{-}C_6$ alkylenyl)-$S(O)_2R^h$, $-(C_1\text{-}C_6$ alkylenyl)-$S(O)_2NR^jR^k$, $-(C_1\text{-}C_6$ alkylenyl)-$C(O)R^h$, $-(C_1\text{-}C_6$ alkylenyl)-$C(O)OR^h$, $-(C_1\text{-}C_6$ alkylenyl)-$C(O)NR^jR^k$, $-(C_1\text{-}C_6$ alkylenyl)-NR^jR^k, $-(C_1\text{-}C_6$ alkylenyl)-$N(R^h)C(O)R^i$, $-(C_1\text{-}C_6$ alkylenyl)-$N(R^h)S(O)_2R^i$, $-(C_1\text{-}C_6$ alkylenyl)-$N(R^h)C(O)O(R^i)$, $-(C_1\text{-}C_6$ alkylenyl)-$N(R^h)C(O)NR^jR^k$, or $-(C_1\text{-}C_6$ alkylenyl)-CN;

R^h, R^j, R^k, at each occurrence, are each independently hydrogen, $C_1\text{-}C_6$ alkyl, or $C_1\text{-}C_6$ haloalkyl; and

R^i, at each occurrence, is independently $C_1\text{-}C_6$ alkyl or $C_1\text{-}C_6$ haloalkyl.

In another aspect, the present invention provides for methods for treating or preventing disorders that are ameliorated by inhibition of BET. Such methods comprise of administering to the subject a therapeutically effective amount of a compound of formula (I), alone, or in combination with a pharmaceutically acceptable carrier.

Some of the methods are directed to treating or preventing an inflammatory disease or cancer or AIDS.

In another aspect, the present invention relates to methods of treating cancer in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the cancer is selected from the group consisting of: acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma,

hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenström's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In certain embodiments, the additional therapeutic agent is an anti-cancer agent. In particular embodiments, the additional therapeutic agents are selected from the group consisting of cytarabine, bortezomib, and 5-azacitidine.

In another aspect, the present invention relates to methods of treating a disease or condition in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said disease or condition is selected from the group consisting of: Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease, dermatitis, eczema, giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis, inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis, myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In certain embodiments, the methods

further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present invention relates to methods of treating a chronic kidney disease or condition in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said disease or condition is selected from the group consisting of: diabetic nephropathy, hypertensive nephropathy, HIV-associated nephropathy, glomerulonephritis, lupus nephritis, IgA nephropathy, focal segmental glomerulosclerosis, membranous glomerulonephritis, minimal change disease, polycystic kidney disease and tubular interstitial nephritis. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present invention relates to methods of treating an acute kidney injury or disease or condition in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein said acute kidney injury or disease or condition is selected from the group consisting of: ischemia-reperfusion induced, cardiac and major surgery induced, percutaneous coronary intervention induced, radio-contrast agent induced, sepsis induced, pneumonia induced, and drug toxicity induced. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present invention relates to methods of treating AIDS in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

In another aspect, the present invention relates to methods of treating obesity, dyslipidemia, hypercholesterolemia, Alzheimer's disease, metabolic syndrome, hepatic steatosis, type II diabetes, insulin resistance, diabetic retinopathy or diabetic neuropathy in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In

certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

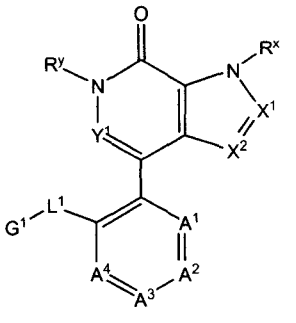
In another aspect, the present invention relates to methods of preventing conception by inhibiting spermatogenesis in a subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In certain embodiments, the methods further comprise administering a therapeutically effective amount of at least one additional therapeutic agent.

A further aspect of the invention provides the use of a compound of formula (I), alone or in combination with a second active pharmaceutical agent, in the manufacture of a medicament for treating or preventing conditions and disorders disclosed herein, with or without a pharmaceutically acceptable carrier.

Pharmaceutical compositions comprising a compound of formula (I), or a pharmaceutically acceptable salt, alone or in combination with a second active pharmaceutical agent, are also provided.

DETAILED DESCRIPTION

Disclosed herein are compounds of formula (I)



(I)

wherein A^1, A^2, A^3, A^4, X^1, X^2, Y^1, L^1, G^1, R^x, and R^y are defined above in the Summary of the Invention and below in the Detailed Description. Further, compositions comprising such compounds and methods for treating conditions and disorders using such compounds and compositions are also disclosed.

Compounds disclosed herein may contain one or more variable(s) that occur more than one time in any substituent or in the formulae herein. Definition of a variable on each occurrence is independent of its definition at another occurrence. Further, combinations of substituents are permissible only if such combinations result in stable compounds. Stable compounds are compounds, which can be isolated from a reaction mixture.

a). Definitions

It is noted that, as used in this specification and the intended claims, the singular form "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a single compound as well as one or more of the same or different compounds, reference to "optionally a pharmaceutically acceptable carrier" refers to a single optional pharmaceutically acceptable carrier as well as one or more pharmaceutically acceptable carriers, and the like.

As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated:

The term "alkenyl" as used herein, means a straight or branched hydrocarbon chain containing from 2 to 10 carbons and containing at least one carbon-carbon double bond, optionally substituted with 1, 2, or 3 halogen atoms. The term "C_2-C_6 alkenyl" means an alkenyl group containing 2-6 carbon atoms. Non-limiting examples of alkenyl include buta-1,3-dienyl, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

The term "alkenylene" means a divalent group derived from a straight or branched chain hydrocarbon of 2 to 4 carbon atoms and contains at least one carbon-carbon double bond. Representative examples of alkenylene include, but are not limited to, -CH=CH- and $-CH_2CH=CH-$.

The term "alkyl" as used herein, means a saturated, straight or branched hydrocarbon chain radical. In some instances, the number of carbon atoms in an alkyl moiety is indicated by the prefix "C_x-C_y", wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6 alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms and "C_1-C_3 alkyl" refers to an alkyl substituent containing from 1 to 3 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-methylpropyl, 1-ethylpropyl, 1,2,2-trimethylpropyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, and *n*-decyl.

The term "alkylene" or "alkylenyl" means a divalent radical derived from a straight or branched, saturated hydrocarbon chain, for example, of 1 to 10 carbon atoms or of 1 to 6 carbon atoms (C_1-C_6 alkylenyl) or of 1 to 4 carbon atoms or of 2 to 3 carbon

atoms (C_2-C_3 alkylenyl). Examples of alkylene and alkylenyl include, but are not limited to, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, and -$CH_2CH(CH_3)CH_2$-.

The term "alkynyl" as used herein, means a straight or branched chain hydrocarbon radical containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond, optionally substituted with 1, 2, or 3 halogen atoms. The term "C_2-C_6 alkynyl" means an alkynyl group of 2 to 6 carbon atoms. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.

The term "aryl" as used herein, means phenyl or a bicyclic aryl. The bicyclic aryl is naphthyl, or a phenyl fused to a monocyclic cycloalkyl, or a phenyl fused to a monocyclic cycloalkenyl. Non-limiting examples of the aryl groups include dihydroindenyl, indenyl, naphthyl, dihydronaphthalenyl, and tetrahydronaphthalenyl. The bicyclic aryls are attached to the parent molecular moiety through any carbon atom contained within the bicyclic ring systems and can be unsubstituted or substituted.

The term "cycloalkyl" as used herein, refers to a radical that is a monocyclic cyclic alkyl, a bicyclic cycloalkyl, or a spiro cycloalkyl. The monocyclic cycloalkyl is a carbocyclic ring system containing three to eight carbon atoms, zero heteroatoms and zero double bonds. Examples of monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The bicyclic cycloalkyl is a monocyclic cycloalkyl fused to a monocyclic cycloalkyl ring. The monocyclic and the bicyclic cycloalkyl groups may contain one or two alkylene bridges, each consisting of one, two, three, or four carbon atoms in length, and each bridge links two non-adjacent carbon atoms of the ring system. Non-limiting examples of bicyclic ring systems include bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane, tricyclo[3.3.1.$0^{3,7}$]nonane (octahydro-2,5-methanopentalene or noradamantane), and tricyclo[3.3.1.$1^{3,7}$]decane (adamantane). A spiro cycloalkyl is a monocyclic cycloalkyl wherein two substituents on the same carbon atom of the monocyclic cycloalkyl ring together with said carbon atom form a second monocyclic cycloalkyl ring. The monocyclic, the bicyclic, and the spiro cycloalkyl groups can be unsubstituted or substituted, and are attached to the parent molecular moiety through any substitutable atom contained within the ring system.

The term "cycloalkenyl" as used herein, refers to a monocyclic or a bicyclic hydrocarbon ring radical. The monocyclic cycloalkenyl has four-, five-, six-, seven- or eight carbon atoms and zero heteroatoms. The four-membered ring systems have one

double bond, the five-or six-membered ring systems have one or two double bonds, and the seven- or eight-membered ring systems have one, two, or three double bonds. Representative examples of monocyclic cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. The bicyclic cycloalkenyl is a monocyclic cycloalkenyl fused to a monocyclic cycloalkyl group, or a monocyclic cycloalkenyl fused to a monocyclic cycloalkenyl group. The monocyclic or bicyclic cycloalkenyl ring may contain one or two alkylene bridges, each consisting of one, two, or three carbon atoms, and each linking two non-adjacent carbon atoms of the ring system. Representative examples of the bicyclic cycloalkenyl groups include, but are not limited to, 4,5,6,7-tetrahydro-3aH-indene, octahydronaphthalenyl, and 1,6-dihydro-pentalene. The monocyclic and bicyclic cycloalkenyls can be attached to the parent molecular moiety through any substitutable atom contained within the ring systems, and can be unsubstituted or substituted.

The term "halo" or "halogen" as used herein, means Cl, Br, I, and F.

The term "haloalkyl" as used herein, means an alkyl group, as defined herein, in which one, two, three, four, five or six hydrogen atoms are replaced by halogen. The term "C_1-C_6 haloalkyl" means a C_1-C_6 alkyl group, as defined herein, in which one, two, three, four, five or six hydrogen atoms are replaced by halogen. The term "C_1-C_3 haloalkyl" means a C_1-C_3 alkyl group, as defined herein, in which one, two, or three hydrogen atoms are replaced by halogen. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, 2-chloro-3-fluoropentyl, trifluorobutyl, and trifluoropropyl.

The term "heterocycle" or "heterocyclic" as used herein, means a radical of a monocyclic heterocycle, a bicyclic heterocycle, and a spiro heterocycle. A monocyclic heterocycle is a three-, four-, five-, six-, seven-, or eight-membered carbocyclic ring also containing at least one heteroatom independently selected from the group consisting of O, N, and S. A three- or four-membered ring contains zero or one double bond, and one heteroatom selected from the group consisting of O, N, and S. When two O atoms or one O atom and one S atom are present in a heterocyclic ring, then the two O atoms or one O atom and one S atom are not bonded directly to each other. A five-membered ring contains zero or one double bond and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Examples of five-membered heterocyclic rings include those containing in the ring: 1 O; 1 S; 1 N; 2 N; 3 N; 1 S and 1 N; 1 S, and 2 N; 1 O and 1

N; or 1 O and 2 N. Examples of 5-membered heterocyclic groups include tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, imidazolidinyl, oxazolidinyl, imidazolinyl, isoxazolidinyl, pyrrolidinyl, 2-pyrrolinyl, and 3-pyrrolinyl. A six-membered ring contains zero, one, or two double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Examples of six-membered heterocyclic rings include those containing in the ring: 1 O; 2 O; 1 S; 2 S; 1 N; 2 N; 3 N; 1 S, 1 O, and 1 N; 1 S and 1 N; 1 S and 2 N; 1 S and 1 O; 1 S and 2 O; 1 Q and 1 N; and 1 O and 2 N. Examples of 6-membered heterocyclic groups include tetrahydropyranyl, dihydropyranyl, dioxanyl, 1,3-dioxolanyl, 1,4-dithianyl, hexahydropyrimidine, morpholinyl, piperazinyl, piperidinyl, 2H-pyranyl, 4H-pyranyl, pyrazolidinyl, pyrazolinyl, 1,2,3,6-tetrahydropyridinyl, tetrahydrothiopyranyl, 1,1-dioxo-hexahydro-1-thiopyranyl, 1,1-dioxo-1λ^6-thiomorpholinyl, thiomorpholinyl, thioxanyl, and trithianyl. Seven- and eight-membered rings contains zero, one, two, or three double bonds and one, two, or three heteroatoms selected from the group consisting of O, N, and S. Representative examples of monocyclic heterocycles include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, oxetanyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyridinyl, tetrahydropyranyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, thiopyranyl, and trithianyl. The bicyclic heterocycle is a monocyclic heterocycle fused to a phenyl group, or a monocyclic heterocycle fused to a monocyclic cycloalkyl, or a monocyclic heterocycle fused to a monocyclic cycloalkenyl, or a monocyclic heterocycle fused to a monocyclic heterocycle. Representative examples of bicyclic heterocycles include, but are not limited to, benzopyranyl, benzothiopyranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-1H-indolyl, 3,4-dihydroisoquinolin-2(1H)-yl, 2,3,4,6-tetrahydro-1H-pyrido[1,2-a]pyrazin-2-yl, hexahydropyrano[3,4-b][1,4]oxazin-1(5H)-yl. The monocyclic heterocycle and the bicyclic heterocycle may contain one or two alkylene bridges or an alkenylene bridge, or mixture thereof, each consisting of no more than four carbon atoms and each linking two non adjacent atoms of the ring system. Examples of such bridged heterocycle include, but are not limited to, azabicyclo[2.2.1]heptyl (including 2-azabicyclo[2.2.1]hept-2-yl), 8-azabicyclo[3.2.1]oct-8-yl, octahydro-2,5-epoxypentalene, hexahydro-2*H*-2,5-methanocyclopenta[*b*]furan, hexahydro-1*H*-1,4-

methanocyclopenta[*c*]furan, aza-admantane (1-azatricyclo[3.3.1.1^{3,7}]decane), and oxa-adamantane (2-oxatricyclo[3.3.1.1^{3,7}]decane). A spiro heterocycle is a monocyclic heterocycle wherein two substituents on the same carbon atom of the monocyclic heterocycle ring together with said carbon atom form a second ring system selected from a monocyclic cycloalkyl, a bicyclic cycloalkyl, a monocyclic heterocycle, or a bicyclic heterocycle. Examples of spiro heterocycle include, but not limited to, 6-azaspiro[2.5]oct-6-yl, 1'H, 4H-spiro[1,3-benzodioxine-2,4'-piperidin]-1'-yl, 1'H, 3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl, and 1,4-dioxa-8-azaspiro[4.5]dec-8-yl. The monocyclic, the bicyclic, and the spiro heterocycles can be unsubstituted or substituted. The monocyclic, the bicyclic and the spiro heterocycles are connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the ring systems. The nitrogen and sulfur heteroatoms in the heterocycle rings may optionally be oxidized (e.g. 1,1-dioxidotetrahydrothienyl, 1,1-dioxido-1,2-thiazolidinyl, 1,1-dioxidothiomorpholinyl)) and the nitrogen atoms may optionally be quarternized.

The term "heteroaryl" as used herein, means a monocyclic heteroaryl and a bicyclic heteroaryl. The monocyclic heteroaryl is a five- or six-membered ring. The five-membered ring contains two double bonds. The five membered ring may contain one heteroatom selected from O or S; or one, two, three, or four nitrogen atoms and optionally one oxygen or one sulfur atom. The six-membered ring contains three double bonds and one, two, three or four nitrogen atoms. Representative examples of monocyclic heteroaryl include, but are not limited to, furanyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, 1,3-oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, 1,3-thiazolyl, thienyl, triazolyl, and triazinyl. The bicyclic heteroaryl consists of a monocyclic heteroaryl fused to a phenyl, or a monocyclic heteroaryl fused to a monocyclic cycloalkyl, or a monocyclic heteroaryl fused to a monocyclic cycloalkenyl, or a monocyclic heteroaryl fused to a monocyclic heteroaryl, or a monocyclic heteroaryl fused to a monocyclic heterocycle. Representative examples of bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzoxadiazolyl, phthalazinyl, 2,6-dihydropyrrolo[3,4-c]pyrazol-5(4H)-yl, 6,7-dihydro-pyrazolo[1,5-a]pyrazin-5(4H)-yl, 6,7-dihydro-1,3-benzothiazolyl, imidazo[1,2-*a*]pyridinyl, indazolyl, indolyl, isoindolyl, isoquinolinyl, naphthyridinyl, pyridoimidazolyl, quinolinyl, 2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl, thiazolo[5,4-b]pyridin-2-yl, thiazolo[5,4-d]pyrimidin-2-yl, and 5,6,7,8-tetrahydroquinolin-5-yl. The monocyclic and bicyclic heteroaryl groups can be substituted or unsubstituted and are connected to the

parent molecular moiety through any substitutable carbon atom or any substitutable nitrogen atom contained within the ring systems. The nitrogen atom in the heteroaryl rings may optionally be oxidized and may optionally be quarternized.

The term "heteroatom" as used herein, means a nitrogen, oxygen, and sulfur.

The term "oxo" as used herein, means a =O group.

If a moiety is described as "substituted", a non-hydrogen radical is in the place of hydrogen radical of any substitutable atom of the moiety. Thus, for example, a substituted heterocycle moiety is a heterocycle moiety in which at least one non-hydrogen radical is in the place of a hydrogen radical on the heterocycle. It should be recognized that if there are more than one substitution on a moiety, each non-hydrogen radical may be identical or different (unless otherwise stated).

If a moiety is described as being "optionally substituted," the moiety may be either (1) not substituted or (2) substituted. If a moiety is described as being optionally substituted with up to a particular number of non-hydrogen radicals, that moiety may be either (1) not substituted; or (2) substituted by up to that particular number of non-hydrogen radicals or by up to the maximum number of substitutable positions on the moiety, whichever is less. Thus, for example, if a moiety is described as a heteroaryl optionally substituted with up to 3 non-hydrogen radicals, then any heteroaryl with less than 3 substitutable positions would be optionally substituted by up to only as many non-hydrogen radicals as the heteroaryl has substitutable positions. To illustrate, tetrazolyl (which has only one substitutable position) would be optionally substituted with up to one non-hydrogen radical. To illustrate further, if an amino nitrogen is described as being optionally substituted with up to 2 non-hydrogen radicals, then a primary amino nitrogen will be optionally substituted with up to 2 non-hydrogen radicals, whereas a secondary amino nitrogen will be optionally substituted with up to only 1 non-hydrogen radical.

The terms "treat", "treating", and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

The terms "prevent", "preventing", and "prevention" refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from acquiring a disease. As used herein, "prevent", "preventing" and "prevention" also include delaying the onset of a disease and/or its attendant symptoms and reducing a subject's risk of acquiring a disease.

The phrase "therapeutically effective amount" means an amount of a compound, or a pharmaceutically acceptable salt thereof, sufficient to prevent the development of or to

alleviate to some extent one or more of the symptoms of the condition or disorder being treated when administered alone or in conjunction with another pharmaceutical agent or treatment in a particular subject or subject population. For example in a human or other mammal, a therapeutically effective amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular disease and subject being treated.

The term "subject" is defined herein to refer to animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

b. Compounds

Compounds of the invention have the general formula (I) as described above.

Particular values of variable groups in compounds of formula (I) are as follows. Such values may be used where appropriate with any of the other values, definitions, claims or embodiments defined hereinbefore or hereinafter.

In compounds of formula (I), R^x is as defined in the Summary. For example, in certain embodiments, R^x is hydrogen or methyl. In certain embodiments, R^x is hydrogen.

R^y, in compounds of formula (I), is as disclosed in the Summary. For example, in certain embodiments, R^y is C_1-C_3 alkyl (e.g. methyl, ethyl). In certain embodiments, R^y is methyl.

X^1 is as disclosed in the Summary. For example, in certain embodiments, X^1 is N. In certain embodiments, X^1 is CR^{x1}. R^{x1} is as defined in the Summary or embodiments herein. In certain embodiments, R^{x1} is hydrogen, C_2-C_6 alkenyl, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, $-C(O)R^{dx1}$, G^{x1}, or C_1-C_6 alkyl wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax1}, $NR^{bx1}R^{cx1}$, and G^{x1}. In certain embodiments, R^{x1} is hydrogen, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, G^{x1}, or C_1-C_6 alkyl wherein the C_1-C_6 alkyl is optionally substituted with OR^{ax1}. In certain embodiments, R^{x1} is hydrogen, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, optionally substituted phenyl, or C_1-C_6 alkyl wherein the C_1-C_6 alkyl is optionally substituted with OR^{ax1} In certain embodiments, R^{x1} is hydrogen, $-C(O)OR^{ax1}$, or $-C(O)NR^{bx1}R^{cx1}$. In certain embodiments, R^{x1} is hydrogen or unsubstituted C_1-C_6 alkyl. In certain embodiments, R^{x1} is $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, or C_1-C_6 alkyl substituted with OR^{ax1}. In certain embodiments, R^{x1} is hydrogen or $-C(O)NR^{bx1}R^{cx1}$. In certain embodiments, R^{x1} is hydrogen. R^{ax1}, R^{bx1}, R^{cx1}, R^{dx1}, and G^{x1}, are as disclosed in the Summary. For example,

R^{ax1} and R^{bx1}, are each independently hydrogen, C_1-C_6 alkyl (e.g. methyl, ethyl, isopropyl), or C_1-C_6 haloalkyl (e.g. trifluoromethyl). In certain embodiments, R^{ax1} and R^{bx1}, are each independently hydrogen or C_1-C_6 alkyl (e.g. methyl, ethyl, isopropyl). In certain embodiments, R^{ax1} and R^{bx1}, are each independently hydrogen, methyl, or ethyl. R^{cx1}, for example, is hydrogen, C_1-C_6 alkyl (e.g. methyl, ethyl, isopropyl), or C_1-C_6 haloalkyl (e.g. trifluoromethyl, 2,2,2 trifluoroethyl), wherein the C_1-C_6 alkyl is optionally substituted with G^{x1}. In certain embodiments, R^{cx1}, for example, is hydrogen or C_1-C_6 alkyl (e.g. methyl, ethyl, isopropyl). In certain embodiments, R^{cx1}, for example, is G^{x1} or C_1-C_6 alkyl substituted with G^{x1}; wherein G^{x1} is thiazolyl, morpholinyl, piperazinyl, tetrahydrofuranyl, or phenyl, each of which is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl.

X^2 is as disclosed in the Summary. For example, in certain embodiments, X^2 is N. In certain embodiments, X^2 is CR^{x2}. R^{x2} is as defined in the Summary or embodiments herein. In certain embodiments, X^2 is C(O)H or C_1-C_6 alkyl substituted with one G^{x2}. In certain embodiments, X^2 is C(O)H or C_1-C_3 alkyl substituted with one G^{x2} wherein G^{x2} is piperidinyl, piperazinyl, or morpholinyl, each of which is optionally substituted with 1, 2, or 3 C_1-C_3 alkyl. In certain embodiments, R^{x2} is hydrogen or unsubstituted C_1-C_6 alkyl (e.g. methyl). In certain embodiments, R^{x2} is hydrogen.

Y^1 is N or CR^u. For example, in certain embodiments, Y^1 is N. In certain embodiments, Y^1 is CR^u. R^u is as defined in the Summary and embodiments herein. For example, in certain embodiments, R^u is hydrogen or C_1-C_6 alkyl (e.g. methyl). In certain embodiments, R^u is hydrogen or C_1-C_3 alkyl (e.g. methyl). In certain embodiments, R^u is hydrogen or methyl. In certain embodiments, R^u is hydrogen.

A^1, A^2, A^3, and A^4 are as defined in the Summary. In certain embodiments, A^1 is CR^1, A^2 is CR^2, A^3 is CR^3, and A^4 is CR^4; or one of A^1, A^2, A^3, and A^4 is N. In certain embodiments, A^1 is CR^1, A^2 is CR^2, A^3 is CR^3, and A^4 is CR^4. In certain embodiments, one of A^1, A^2, A^3, and A^4 is N. In the embodiments that one of A^1, A^2, A^3, and A^4 is N, example of a group of compound includes, but is not limited to, those wherein A^1 is CR^1, A^2 is CR^2, A^3 is CR^3, and A^4 is N. In certain embodiments, two of A^1, A^2, A^3, and A^4 are N, for example, A^1 is N, A^2 is CR^2, A^3 is N, and A^4 is CR^4; or for example, A^1 is N, A^2 is CR^2, A^3 is CR^3, and A^4 is N. In certain embodiments, three of A^1, A^2, A^3, and A^4 are N, for example, A^1 is N, A^2 is CR^2, A^3 is N, and A^4 is N.

R^1, R^3, and R^4, are as defined in the Summary. For example, in certain embodiments, R^1, R^3, and R^4, are each independently hydrogen, C_1-C_6 alkyl (e.g. methyl,

ethyl), halogen (e.g. Br, F, or Cl), or CN. For example, in certain embodiments, R^1, R^3, and R^4, are each independently hydrogen, C_1-C_6 alkyl (e.g. methyl, ethyl), or C_1-C_6 haloalkyl (e.g. trifluoromethyl). In certain embodiments, R^1, R^3, and R^4, are each independently hydrogen or methyl. In certain embodiments, R^1, R^3, and R^4 are hydrogen.

R^2 is as disclosed in the Summary. In certain embodiment, R^2, for example, is halogen, haloalkyl (e.g. CF_3), or -(C_1-C_3 alkylenyl)-CN. In certain embodiments, R^2, for example, is hydrogen, C_1-C_6 alkyl, NO_2, G^{2a}, $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)OR^{2a}$, $-C(O)NR^{2b}R^{2c}$, $-NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, –($C_1$-$C_6$ alkylenyl)-G^{2a}, –(C_1-C_6 alkylenyl)-OR^{2a}, -(C_1-C_6 alkylenyl)-$S(O)_2R^{2d}$, -(C_1-C_6 alkylenyl)-$S(O)_2NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$C(O)R^{2d}$, –(C_1-C_6 alkylenyl)-$C(O)OR^{2a}$, -(C_1-C_6 alkylenyl)-$C(O)NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)R^{2d}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})S(O)_2R^{2d}$, or –(C_1-C_6 alkylenyl)-$N(R^{2e})S(O)_2NR^{2b}R^{2c}$. In certain embodiments, R^2, for example, is hydrogen, or NO_2. In certain embodiments, R^2, for example, is G^{2a}, $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)OR^{2a}$, $-C(O)NR^{2b}R^{2c}$, $-NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, –($C_1$-$C_6$ alkylenyl)-G^{2a}, –(C_1-C_6 alkylenyl)-OR^{2a}, -(C_1-C_6 alkylenyl)-$S(O)_2R^{2d}$, -(C_1-C_6 alkylenyl)-$S(O)_2NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$C(O)R^{2d}$, –(C_1-C_6 alkylenyl)-$C(O)OR^{2a}$, -(C_1-C_6 alkylenyl)-$C(O)NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)R^{2d}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})S(O)_2R^{2d}$, or –(C_1-C_6 alkylenyl)-$N(R^{2e})S(O)_2NR^{2b}R^{2c}$. In certain embodiments, R^2, for example, is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, -($C_1$-$C_6$ alkylenyl)-$S(O)_2R^{2d}$, -(C_1-C_6 alkylenyl)-$S(O)_2NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$C(O)R^{2d}$, -(C_1-C_6 alkylenyl)-$C(O)NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)R^{2d}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})S(O)_2R^{2d}$, or –(C_1-C_6 alkylenyl)-$N(R^{2e})S(O)_2NR^{2b}R^{2c}$. In certain embodiments, R^2, for example, is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$. In certain embodiment, R^2, for example, is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or -(C_1-C_6 alkylenyl)-$S(O)_2R^{2d}$. In certain embodiment, R^2, for example, is -(C_1-C_3 alkylenyl)-$S(O)_2R^{2d}$ wherein R^{2d} is C_1-C_3 alkyl. In certain embodiment, R^2, for example, is -(CH_2)-$S(O)_2R^{2d}$ wherein R^{2d} is methyl or ethyl.

G^{2a}, R^{2a}, R^{2b}, R^{2c}, R^{2d}, and R^{2e} are as disclosed in the Summary and embodiments herein below.

In the embodiments wherein R^2 is G^{2a}, G^{2a} is as disclosed in the Summary and embodiments herein. For example, in certain embodiments, G^{2a} is an optionally

substituted heterocycle. In certain embodiments, G^{2a} is an optionally substituted monocyclic heterocycle. In certain embodiments, G^{2a} is 1,2-dioxido-1,2-thiazolidin-2-yl or tetrahydropyridinyl, each of which is optionally substituted. In certain embodiments, G^{2a} is optionally substituted 1,2-dioxido-1,2-thiazolidin-2-yl. In certain embodiment, G^{2a} is aryl or heteroaryl, each of which is optionally substituted. In certain embodiments, G^{2a} is optionally substituted phenyl. In certain embodiments, G^{2a} is pyridinyl or pyrazolyl, each of which is optionally substituted. In certain embodiments, G^{2a} is unsubstituted.

In the embodiments wherein R^2 is $-(C_1\text{-}C_6$ alkylenyl)-G^{2a}, G^{2a} is as disclosed in the Summary and embodiments herein. For example, in certain embodiments, G^{2a} is a heterocycle or a heteroaryl, each of which is optionally substituted. In certain embodiments, G^{2a} is a monocyclic heterocycle or a monocyclic heteroaryl, each of which is optionally substituted. In certain embodiments, G^{2a} is 1,1-dioxido-1,2-thiazolidin-2-yl, pyrrolidinyl, morpholinyl, or pyrazolyl, each of which is optionally substituted. In certain embodiments, G^{2a} is unsubstituted. In certain embodiments, G^{2a} is optionally substituted phenyl.

Where G^{2a} group is optionally substituted, it is, for example, optionally substituted with 1, 2, 3, 4, or 5 R^v. R^v is as described in the Summary and herein, for example, R^v is $C_1\text{-}C_6$ alkyl (e.g. methyl), halogen (e.g. F, Cl), $C_1\text{-}C_6$ haloalkyl, -CN, $-NR^jR^k$, or $-C(O)OR^h$; or for example, R^v is $C_1\text{-}C_6$ alkyl (e.g. methyl), halogen (e.g. F, Cl), or $C_1\text{-}C_6$ haloalkyl.

In the embodiments wherein R^2 is $-S(O)_2R^{2d}$, R^{2d} is as disclosed in the Summary and embodiments herein. In certain embodiments, R^{2d} is $C_1\text{-}C_6$ haloalkyl (e.g. CF_3), G^{2b}, unsubstituted $C_1\text{-}C_6$ alkyl (e.g. methyl, ethyl, isopropyl), or $C_1\text{-}C_6$ alkyl substituted with one G^{2b} group; wherein G^{2b} is phenyl, monocyclic cycloalkyl, or monocyclic heterocycle, each of which is optionally substituted. In some such embodiments, the G^{2b} group is optionally substituted with 1, 2, or 3 R^v groups wherein R^v is as described in the Summary and herein, for example, each R^v is independently $C_1\text{-}C_6$ alkyl (e.g. methyl), halogen (e.g. F, Cl), $C_1\text{-}C_6$ haloalkyl, $-OR^h$, -CN, or $-NR^jR^k$, In certain embodiments, R^{2d} is $C_1\text{-}C_6$ haloalkyl or unsubstituted $C_1\text{-}C_6$ alkyl. In certain embodiments, R^{2d} is methyl or ethyl.

In the embodiments wherein R^2 is $-S(O)_2NR^{2b}R^{2c}$, R^{2b} and R^{2c} are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2b} is hydrogen or unsubstituted $C_1\text{-}C_6$ alkyl (e.g. methyl, ethyl), and R^{2c} is hydrogen, unsubstituted $C_1\text{-}C_6$ alkyl (e.g. methyl, ethyl), or $C_1\text{-}C_6$ haloalkyl (e.g. 2,2,2-trifluoroethyl, 2-fluoroethyl). In certain embodiments, R^{2b} is hydrogen, and R^{2c} is optionally substituted

phenyl, or R^{2c} is $-C_1$-C_3 alkyl substituted with one G^{2b} group wherein G^{2b} is optionally substituted pyridinyl.

In the embodiments wherein R^2 is $-C(O)R^{2d}$, R^{2d} is as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2d} is G^{2b} wherein G^{2b} is as disclosed in the Summary and embodiments herein. For example, in certain embodiments, G^{2b} is an optionally substituted heterocycle. In certain embodiments, G^{2b} is an optionally substituted monocyclic heterocycle. In certain embodiments, G^{2b} is 1,1-dioxidothiomorpholin-4-yl, piperazinyl, piperidinyl, pyrrolidin-1-yl, or morpholin-4-yl, each of which is optionally substituted. Each G^{2b} is optionally substituted as described in the Summary and embodiments herein. For example, each G^{2b} is independently unsubstituted or substituted with 1, 2, or 3 R^v. R^v is as described in the Summary and embodiments herein. For example, each R^v is independently C_1-C_6 alkyl (e.g. methyl), oxo, $N(H)C(O)O(C_1$-C_6 alkyl), $-CH_2$-$C(O)NR^jR^k$, -C(O)-monocyclic heterocycle, or –C(O)-monocyclic heteroaryl. In certain embodiments, each R^v is independently C_1-C_6 alkyl (e.g. methyl), oxo, or $N(H)C(O)O(C_1$-C_6 alkyl).

In the embodiments wherein R^2 is $-C(O)OR^{2a}$, R^{2a} is as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2a} is hydrogen or unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl).

In the embodiments wherein R^2 is $-C(O)NR^{2b}R^{2c}$, R^{2b} and R^{2c} are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2b} is hydrogen or unsubstituted C_1-C_6 alkyl (e.g. methyl), and R^{2c} is hydrogen, G^{2b}, C_1-C_6 haloalkyl (e.g. 2,2-difluoroethyl), C_1-C_6 alkyl (e.g. methyl, ethyl) wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of $-OR^{z1}$, $NR^{z1}R^{z2}$, and G^{2b}. R^{z1}, R^{z2}, and G^{2b} are as defined in the Summary and embodiments herein. For example, in certain embodiments, G^{2b} is optionally substituted phenyl. In certain embodiments, G^{2b} is a cycloalkyl, a heteroaryl, or a heterocycle, each of which is optionally substituted. In certain embodiments, G^{2b} is a monocyclic cycloalkyl, a monocyclic heteroaryl, or a monocyclic heterocycle, each of which is optionally substituted. In certain embodiments, G^{2b} is pyridinyl, pyrimidinyl, indazolyl, indolyl, cyclopentyl, thiazolyl, 1,1-dioxidotetrahydrothienyl, tetrahydrofuranyl, piperazinyl, piperidinyl, or pyrrolidinyl, each of which is optionally substituted. Each G^{2b} is optionally substituted as described in the Summary and embodiments herein. For example, each G^{2b} is independently unsubstituted or substituted with 1, 2, or 3 R^v. R^v is as described in the Summary and embodiments herein. For example, each R^v is independently C_1-C_6 alkyl

(e.g. methyl), C_1-C_6 haloalkyl, -OR^h, -$C(O)OR^h$, -$S(O)_2R^h$, halogen, or oxo. In certain embodiments, each R^v is independently C_1-C_6 alkyl (e.g. methyl) or oxo.

In the embodiments wherein R^2 is -$NR^{2b}R^{2c}$, R^{2b} and R^{2c} are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2b} and R^{2c} are each independently hydrogen or unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl).

In the embodiments wherein R^2 is -$N(R^{2e})C(O)R^{2d}$, R^{2d} and R^{2e} are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2e} hydrogen or unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl), and R^{2d} is unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl, tert-butyl) or C_1-C_6 haloalkyl (e.g. 2,2,2-trifluoroethyl).

In the embodiments wherein R^2 is -$N(R^{2e})S(O)_2R^{2d}$, R^{2d} and R^{2e} are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2e} is hydrogen or unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl), and R^{2d} is unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl) or C_1-C_6 haloalkyl (e.g. 2,2,2-trifluoroethyl, 2-fluoroethyl, 2,2-dfluoroethyl). In certain embodiments, R^{2e} is hydrogen and R^{2d} is unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl). In certain embodiments, R^{2e} is C_1-C_6 haloalkyl, or C_1-C_6 alkyl substituted with one substituent selected from the group consisting of –OR^{z1}, -$NR^{z1}R^{z2}$, and G^{2b}, and R^{2d} is unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl). In certain embodiments, R^{2e} is C_1-C_6 haloalkyl (e.g. 3,3,3-trifluoropropyl), or C_1-C_3 alkyl substituted with one substituent selected from the group consisting of –OR^{z1}, -$NR^{z1}R^{z2}$, and G^{2b}, and R^{2d} is unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl), wherein G^{2b} is monocyclic cycloalkyl (e.g. cyclopropyl), monocyclic heterocycle (e.g. pyrrolidinylor tetrahydrofuranyl), or monocyclic heteroaryl (e.g. pyridinyl), each of which is optionally substituted.

In the embodiments wherein R^2 is -$N(R^{2e})S(O)_2NR^{2b}R^{2c}$, R^{2b}, R^{2c}, and R^{2e} are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2b}, R^{2c}, and R^{2e} are each independently hydrogen or unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl).

In the embodiments wherein R^2 is –(C_1-C_6 alkylenyl)-OR^{2a}, R^{2a} is as described in the Summary and embodiments herein. In certain embodiments R^{2a} is hydrogen. In certain embodiments, R^2 is –CH_2-OH or –CH_2CH_2-OH.

In the embodiments wherein R^2 is –(C_1-C_6 alkylenyl)-$C(O)OR^{2a}$, R^{2a} is as described in the Summary and embodiments herein. For example, R^{2a} is hydrogen or unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl).

In the embodiments wherein R^2 is -(C_1-C_6 alkylenyl)-$C(O)NR^{2b}R^{2c}$, R^{2b} and R^{2c} are as disclosed in the Summary and embodiments herein. For example, in certain

embodiments, R^{2b} and R^{2c} are each independently hydrogen or unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl).

In the embodiments wherein R^2 is -(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)R^{2d}$, R^{2d} and R^{2e} are as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2e} is hydrogen or unsubstituted C_1-C_6 alkyl (e.g. methyl, ethyl), and R^{2d} is C_1-C_6 alkyl (e.g. methyl) optionally substituted with $C(O)OR^{z1}$.

In the embodiments wherein R^2 is -(C_1-C_6 alkylenyl)-$S(O)_2R^{2d}$, R^{2d} is as disclosed in the Summary and embodiments herein. For example, in certain embodiments, R^{2d} is optionally substituted phenyl or unsubstituted C_1-C_6 alkyl. In certain embodiments, R^{2d} is unsubstituted C_1-C_3 alkyl. In certain embodiments, R^{2d} is methyl or ethyl. In certain embodiments, R^{2d} is optionally substituted phenyl.

L^1 is as set forth in the Summary and embodiments herein. For example, in certain embodiments, L^1 is absent, CH_2, C(H)(OH), C(O), $(CH_2)_mO$, or $(CH_2)_mN(R^z)$. For example, in certain embodiments, L^1 is CH_2, C(O), $(CH_2)_mO$, or $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mO$ or $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mO$. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$.

The variable, m, is 0 or 1. In certain embodiments, m is 0. In certain embodiments, m is 1.

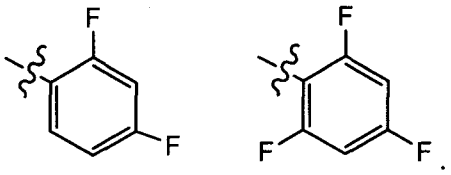
R^z, is as set forth in the Summary and embodiments herein. For example, R^z is hydrogen or C_1-C_3 alkyl. In certain embodiments, R^z is hydrogen.

G^1 is as set forth in the Summary and embodiments herein. For example, G^1 is G^{1a}. In certain embodiments, G^1 is –(C_1-C_6 alkylenyl)-G^{1a}. In certain embodiments, G^1 is C_1-C_6 alkyl or alkoxyalkyl. In certain embodiments, G^1 is C_1-C_6 alkyl (e.g. methyl, ethyl, isobutyl, or 2,2-dimethylpropyl). In certain embodiments, G^1 is alkoxyalkyl.

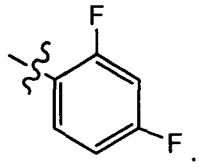
G^{1a} is as defined in the Summary and embodiments herein. For example, in certain embodiments G^{1a} is aryl, heterocycle, or cycloalkyl, each of which is optionally substituted. In certain embodiments G^{1a} is aryl, heterocycle, heteroaryl, or cycloalkyl, each of which is optionally substituted. In certain embodiments G^{1a} is optionally substituted aryl. In certain embodiments G^{1a} is optionally substituted heterocycle. In certain embodiments G^{1a} is optionally substituted heteroaryl. In certain embodiments G^{1a} is optionally substituted cycloalkyl.

In the embodiments wherein G^{1a} is optionally substituted aryl, G^{1a}, for example, is phenyl, naphthyl, or indanyl, each of which is optionally substituted. In certain embodiments, G^{1a}, for example, is optionally substituted phenyl. In certain embodiments,

G^{1a}, for example, is phenyl optionally substituted with one or two halogen (e.g. F). In certain embodiments, G^{1a} is



In certain embodiments, G^{1a} is unsubstituted phenyl or



In the embodiments wherein G^{1a} is optionally substituted heterocycle, examples of the heterocycle include, but are not limited to, oxetanyl, tetrahydrofuranyl (e.g. tetrahydrofuran-2-yl, tetrahydrofuran-3-yl), pyrrolidinyl, morpholinyl, piperidinyl, tetrahydrothiopyranyl, and tetrahydropyranyl (e.g. tetrahydropyran-4-yl, tetrahydropyran-3-yl), each of which (including the exemplary rings) is optionally substituted.

In the embodiments wherein G^{1a} is optionally substituted heteroaryl, G^{1a}, for example, is pyrazolyl, pyridinyl, pyrimidinyl, 2,1,3-benzothiadiazolyl, quinolinyl, or isoquinolinyl, each of which is optionally substituted.

In the embodiments wherein G^{1a} is optionally substituted cycloalkyl (e.g. optionally substituted monocyclic cycloalkyl), examples of the cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl, and adamantyl, each of which is optionally substituted. In certain embodiments, G^{1a} is optionally substituted cycloalkyl. In certain embodiments, G^{1a} is unsubstituted cycloalkyl. In certain embodiments, G^{1a} is a substituted cycloalkyl. In certain embodiments, G^{1a} is cyclohexyl optionally substituted with 1 or two substituents selected from the group consisting of C_1-C_3 alkyl (e.g. methyl), O(C_1-C_3 alkyl), and halogen. In certain embodiments, G^{1a} is cyclohexyl optionally substituted with 1 or two substituents selected from the group consisting of methyl and O(CH_3). In certain embodiments, G^{1a} is 4,4-difluorocyclohexyl. In certain embodiments, G^{1a} is optionally substituted cyclopropyl. In certain embodiments, G^{1a} is unsubstituted cyclopropyl.

The optional substituents of G^{1a} are as set forth in the Summary and embodiments herein. For example, each G^{1a} is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 R^w. In certain embodiments, R^w is, for example, C_1-C_6 alkyl -CN, halogen (e.g. F, Cl), oxo, C_1-C_6 haloalkyl (e.g. trifluoromethyl), -OR^h, NR^jR^k, -$S(O)_2R^h$, -$C(O)R^h$,

$-C(O)OR^h$, $-C(O)NR^jR^k$, $-(C_1-C_3$ alkylenyl)$-OR^h$, or $-(C_1-C_3$ alkylenyl)$C(O)NR^jR^k$. In certain embodiments, R^w is, for example, C_1-C_6 alkyl, -CN, halogen (e.g. F, Cl), or C_1-C_6 haloalkyl (e.g. trifluoromethyl). In certain embodiments, R^w is halogen, $-OR^h$, or C_1-C_6 alkyl. In certain embodiments, R^w is halogen. In certain embodiments, R^w is F.

It is appreciated that compounds of formula (I) with combinations of the above embodiments, including particular, more particular and preferred embodiments are contemplated. All embodiments of compounds of formula (I) formed by combining the substituent embodiments discussed above are within the scope of Applicants' invention, and some illustrative embodiments of the compounds of formula (I) are provided below.

Accordingly, one aspect of the invention is directed to a group of compounds of formula (I) wherein L^1 is $(CH_2)_mO$ and G^1 is G^{1a} and G^{1a} is as disclosed in the Summary and embodiments herein above.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1}; and X^2 is CR^{x2}.

Yet other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1}; X^2 is CR^{x2}, and R^y is methyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, and L^1 is CH_2, C(O), $(CH_2)_mO$, or $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mO$. In yet othe embodiments, L^1 is $(CH_2)_mO$ and m is 0. In yet othe embodiments, L^1 is $(CH_2)_mO$ and m is 1. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$ and m is 0. In yet othe embodiments, L^1 is $(CH_2)_mN(R^z)$ and m is 1. R^z has values as described in the Summary and embodiments herein above.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is $-(C_1-C_6$ alkylenyl)$-G^{1a}$ wherein G^{1a} is optionally substituted phenyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is $-(C_1-C_6$ alkylenyl)$-G^{1a}$ wherein G^{1a} is optionally substituted cycloalkyl. In some embodiments, G^{1a} is unsubstituted cyclopropyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is G^{1a}.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted aryl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted phenyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted cycloalkyl (e.g. optionally substituted monocyclic cycloalkyl).

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is N; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted heterocycle (e.g. optionally substituted monocyclic heterocycle).

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; and X^2 is CR^{x2}.

Yet other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, and R^y is methyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, and L^1 is CH_2, C(O), $(CH_2)_mO$, or $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mO$. In yet othe embodiments, L^1 is $(CH_2)_mO$ and m is 0. In yet othe embodiments, L^1 is $(CH_2)_mO$ and m is 1. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$ and m is 0. In yet othe embodiments, L^1 is $(CH_2)_mN(R^z)$ and m is 1. R^z has meaning as described in the Summary and embodiments herein above.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mN(R^z)$, and G^1 is G^{1a} or $-(C_1\text{-}C_6$ alkylenyl)-G^{1a} wherein G^{1a} is phenyl, monocyclic heterocycle (e.g. tetrahydrofuranyl), or monocyclic cycloalkyl (e.g. cyclopropyl, cyclopentyl, cyclohexyl), each of which (including the exemplary rings) is optionally substituted.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mN(R^z)$, m is 0, R^z is hydrogen, and G^1 is G^{1a} wherein G^{1a} is phenyl, monocyclic heterocycle (e.g. tetrahydrofuranyl), or monocyclic cycloalkyl (e.g. cyclopropyl, cyclopentyl, cyclohexyl), each of which (including the exemplary rings) is optionally substituted.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mN(R^z)$, m is 0, R^z is hydrogen, and G^1 is $-(C_1\text{-}C_6$ alkylenyl)-G^{1a} wherein G^{1a} is monocyclic heterocycle (e.g. tetrahydrofuranyl), or monocyclic cycloalkyl (e.g. cyclopropyl, cyclopentyl, cyclohexyl), each of which (including the exemplary rings) is optionally substituted. In some embodiments, G^1 is $-(C_1\text{-}C_3$ alkylenyl)-G^{1a} wherein G^{1a} is optionally substituted monocyclic cycloalkyl (e.g. cyclopropyl, cyclopentyl, cyclohexyl, each of which is optionally substituted). In some embodiments, G^1 is $-(CH_2)$-G^{1a} wherein G^{1a} is optionally substituted monocyclic cycloalkyl (e.g. cyclopropyl, cyclopentyl, cyclohexyl, each of which is optionally substituted). In certain embodiments, G^{1a} is optionally substituted is monocyclic heterocycle (e.g. optionally substituted tetrahydrofuranyl). In certain embodiments, G^{1a} is optionally substituted cyclopropyl. In some embodiments, G^{1a} is unsubstituted cyclopropyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is $C_1\text{-}C_6$ alkyl or alkoxyalkyl. In certain embodiments, G^1 is $C_1\text{-}C_6$ alkyl (e.g. methyl, ethyl, isobutyl, or 2,2-dimethylpropyl). In certain embodiments, G^1 is alkoxyalkyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is $-(C_1\text{-}C_6$ alkylenyl)-G^{1a} wherein G^{1a} is optionally substituted phenyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is $-(C_1\text{-}C_6$ alkylenyl)-G^{1a} wherein G^{1a} is optionally substituted cycloalkyl. In some embodiments, G^{1a} is optionally substituted cyclopropyl. In some embodiments, G^{1a} is unsubstituted cyclopropyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is G^{1a}.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted aryl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted phenyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted cycloalkyl (e.g. optionally substituted monocyclic cycloalkyl).

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is CR^{x1}; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted heterocycle (e.g. optionally substituted monocyclic heterocycle).

Yet other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is N; X^2 is CR^{x2}, and R^y is methyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is N; X^2 is CR^{x2}, R^y is methyl, and L^1 is CH_2, C(O), $(CH_2)_mO$, or $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mO$. In yet othe embodiments, L^1 is $(CH_2)_mO$ and m is 0. In yet othe embodiments, L^1 is $(CH_2)_mO$ and m is 1. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$. In certain embodiments, L^1 is $(CH_2)_mN(R^z)$ and m is 0. In yet othe embodiments, L^1 is $(CH_2)_mN(R^z)$ and m is 1. R^z has meaning as described in the Summary and embodiments herein above.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is N; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is G^{1a}.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is N; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted aryl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is N; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted phenyl.

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is N; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted cycloalkyl (e.g. optionally substituted monocyclic cycloalkyl).

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is N; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, G^1 is G^{1a}, and G^{1a} is optionally substituted heterocycle (e.g. optionally substituted monocyclic heterocycle).

Other examples of a group of compounds of formula (I) is directed to those wherein Y^1 is CR^u; X^1 is N; X^2 is CR^{x2}, R^y is methyl, L^1 is $(CH_2)_mO$, and G^1 is $-(C_1\text{-}C_6$ alkylenyl)-G^{1a} wherein G^{1a} is optionally substituted cycloalkyl. In some embodiments, G^{1a} is optionally substituted cyclopropyl. In some embodiments, G^{1a} is unsubstituted cyclopropyl.

Within each group of compounds of formula (I) described herein above, A^1, A^2, A^3, and A^4 have meanings as disclosed in the Summary and embodiments herein above.

For example, within each group of compounds of formula (I) described herein above, examples of a subgroup include those wherein A^1 is CR^1, A^2 is CR^2, A^3 is CR^3, and A^4 is CR^4; or one of A^1, A^2, A^3, and A^4 is N.

Other examples of a subgroup include, but are not limited to, those wherein A^1 is CR^1, A^2 is CR^2, A^3 is CR^3, and A^4 is CR^4.

Other examples of a subgroup include, but are not limited to, those wherein one of A^1, A^2, A^3, and A^4 is N.

Yet other examples of a subgroup include, but are not limited to, those wherein A^1 is CR^1, A^2 is CR^2, A^3 is CR^3, and A^4 is N.

Yet other examples of a subgroup include, but are not limited to, those wherein two of A^1, A^2, A^3, and A^4 are N.

Yet other examples of a subgroup include, but are not limited to, those wherein A^1 is N, A^2 is CR^2, A^3 is N, and A^4 is CR^4.

Yet other examples of a subgroup include, but are not limited to, those wherein A^1 is N, A^2 is CR^2, A^3 is CR^3, and A^4 is N.

Yet other examples of a subgroup include, but are not limited to, those wherein three of A^1, A^2, A^3, and A^4 are N.

Yet other examples of a subgroup include, but are not limited to, those wherein A^1 is N, A^2 is CR^2, A^3 is N, and A^4 is N.

Of all the groups and subgroups of compounds of formula (I) disclosed in the preceding paragraphs, R^1, R^2, R^3, R^4, R^x, R^u; R^{x1}, R^{x2}, m, and the optional substituents of G^1 are as described in the Summary and embodiments herein above.

For example, of all the groups and subgroups of compounds of formula (I) disclosed in the preceding paragraphs, R^2 is hydrogen, C_1-C_6 alkyl, NO_2, G^{2a}, $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)OR^{2a}$, $-C(O)NR^{2b}R^{2c}$, $-NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, $-(C_1$-C_6 alkylenyl)-G^{2a}, $-(C_1$-C_6 alkylenyl)-OR^{2a}, $-(C_1$-C_6 alkylenyl)-$S(O)_2R^{2d}$, $-(C_1$-C_6 alkylenyl)-$S(O)_2NR^{2b}R^{2c}$, $-(C_1$-C_6 alkylenyl)-$C(O)R^{2d}$, $-(C_1$-C_6 alkylenyl)-$C(O)OR^{2a}$, $-(C_1$-C_6 alkylenyl)-$C(O)NR^{2b}R^{2c}$, $-(C_1$-C_6 alkylenyl)-$NR^{2b}R^{2c}$, $-(C_1$-C_6 alkylenyl)-$N(R^{2e})C(O)R^{2d}$, $-(C_1$-C_6 alkylenyl)-$N(R^{2e})S(O)_2R^{2d}$, or $-(C_1$-C_6 alkylenyl)-$N(R^{2e})S(O)_2NR^{2b}R^{2c}$. In certain embodiments, R^2 is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$.

In some embodiments, R^2 is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or $-(C_1\text{-}C_6$ alkylenyl)$-S(O)_2R^{2d}$.

For example, of all the groups and subgroups of compounds of formula (I) disclosed in the preceding paragraphs, R^2 is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, and R^x is hydrogen or methyl. In certain embodiments, R^x is hydrogen.

For example, of all the groups and subgroups of compounds of formula (I) disclosed in the preceding paragraphs, R^2 is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, R^x is hydrogen, and R^{x1} is hydrogen, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, G^{x1}, or C_1-C_6 alkyl wherein the C_1-C_6 alkyl is optionally substituted with OR^{ax1}. In certain embodiments, R^{x1} is hydrogen, $-C(O)OR^{ax1}$, or $-C(O)NR^{bx1}R^{cx1}$.

For example, of all the groups and subgroups of compounds of formula (I) disclosed in the preceding paragraphs, R^2 is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, R^x is hydrogen, R^{x1} is hydrogen, $-C(O)OR^{ax1}$, or $-C(O)NR^{bx1}R^{cx1}$, and R^{x2} is hydrogen.

For example, of all the groups and subgroups of compounds of formula (I) disclosed in the preceding paragraphs, R^2 is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or $-(C_1\text{-}C_6$ alkylenyl)$S(O)_2R^{2d}$, R^x is hydrogen, R^{x1} is hydrogen or $-C(O)NR^{bx1}R^{cx1}$, and R^{x2} is hydrogen.

One aspect of the invention is directed to compounds of formula (I) or pharmaceutically acceptable salts thereof, wherein

R^x is hydrogen;

R^y is methyl;

Y^1 is CR^u wherein R^u is hydrogen;

X^1 is CR^{x1} wherein R^{x1} is hydrogen or $-C(O)NR^{bx1}R^{cx1}$;

X^2 is CR^{x2} wherein R^{x2} is hydrogen;

L^1 is $(CH_2)_mO$ wherein m is 0;

G^1 is G^{1a} or $-(C_1\text{-}C_6$ alkylenyl)$-G^{1a}$, wherein G^{1a} is optionally substituted phenyl or optionally substituted cycloalkyl; and

R^2 is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or $-(C_1\text{-}C_6$ alkylenyl)$-S(O)_2R^{2d}$.

In some such embodiments, A^1 is CR^1, A^2 is CR^2, A^3 is CR^3, and A^4 is CR^4. In some further embodiments, A^1 is CR^1, A^2 is CR^2, A^3 is CR^3, and A^4 is N.

Another aspect of the invention is directed to compounds of formula (I) or pharmaceutically acceptable salts thereof, wherein

R^x is hydrogen;

R^y is methyl;

Y^1 is CR^u wherein R^u is hydrogen;

X^1 is CR^{x1} wherein R^{x1} is hydrogen;

X^2 is CR^{x2} wherein R^{x2} is hydrogen;

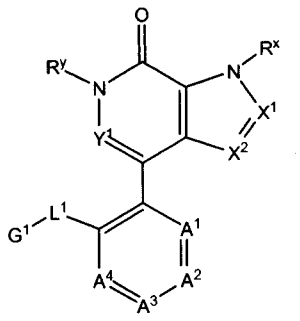
L^1 is $(CH_2)_mN(R^z)$ or wherein m is 0 and R^z is hydrogen;

G^1 is $-(C_1\text{-}C_6$ alkylenyl)-G^{1a}, wherein G^{1a} is optionally substituted cycloalkyl; and

R^2 is $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2R^{2d}$, or $-(C_1\text{-}C_6$ alkylenyl)-$S(O)_2R^{2d}$.

In some such embodiments, A^1 is CR^1, A^2 is CR^2, A^3 is CR^3, and A^4 is CR^4. In some further embodiments, A^1 is CR^1, A^2 is CR^2, A^3 is CR^3, and A^4 is N.

In one aspect the present invention provides for compounds of formula (I) or pharmaceutically acceptable thereof,



(I)

wherein

R^x is hydrogen or C_1-C_3 alkyl;

R^y is C_1-C_3 alkyl, -(C_2-C_3 alkylenyl)-OH, or C_1-C_3 haloalkyl;

X^1 is N or CR^{x1} wherein

R^{x1} is hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, $-C(O)R^{dx1}$, $S(O)_2R^{dx1}$, $-S(O)_2NR^{bx1}R^{cx1}$, G^{x1}, C_1-C_6 haloalkyl, or C_1-C_6 alkyl; wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax1}, SR^{ax1}, $S(O)R^{dx1}$, $S(O)_2R^{dx1}$, $NR^{bx1}R^{cx1}$, $-C(O)R^{ax1}$, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, $-S(O)_2NR^{bx1}R^{cx1}$, and G^{x1};

R^{ax1}, R^{bx1}, and R^{cx1}, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^a, or -(C_1-C_6 alkylenyl)-G^a;

R^{dx1}, at each occurrence, are each independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^a, or -(C_1-C_6 alkylenyl)-G^a;

X^2 is N or CR^{x2}; wherein

R^{x2} is hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -$C(O)OR^{ax2}$, -$C(O)NR^{bx2}R^{cx2}$, -$C(O)R^{dx2}$, $S(O)_2R^{dx2}$, -$S(O)_2NR^{bx2}R^{cx2}$, G^{x2}, C_1-C_6 haloalkyl, or C_1-C_6 alkyl; wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax2}, SR^{ax2}, $S(O)R^{dx2}$, $S(O)_2R^{dx2}$, $NR^{bx2}R^{cx2}$, -$C(O)R^{ax2}$, -$C(O)OR^{ax2}$, -$C(O)NR^{bx2}R^{cx2}$, -$S(O)_2NR^{bx2}R^{cx2}$, and G^{x2};

R^{ax2}, R^{bx2}, and R^{cx2}, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^b, or -(C_1-C_6 alkylenyl)-G^b;

R^{dx2}, at each occurrence, is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^b, or -(C_1-C_6 alkylenyl)-G^b;

Y^1 is N or CR^u; wherein R^u is hydrogen, C_1-C_6 alkyl, halogen, or C_1-C_6 haloalkyl;

A^1 is N or CR^1, A^2 is N or CR^2, A^3 is N or CR^3; and A^4 is N or CR^4; with the proviso that zero, one, two, or three of A^1, A^2, A^3, and A^4 are N;

R^1, R^3, and R^4 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, CN, or NO_2;

R^2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, -CN, NO_2, G^{2a}, -OR^{2a}, -$OC(O)R^{2d}$, -$OC(O)NR^{2b}R^{2c}$, -SR^{2a}, -$S(O)_2R^{2d}$, -$S(O)_2NR^{2b}R^{2c}$, -$C(O)R^{2d}$, -$C(O)OR^{2a}$, -$C(O)NR^{2b}R^{2c}$, -$NR^{2b}R^{2c}$, -$N(R^{2e})C(O)R^{2d}$, -$N(R^{2e})S(O)_2R^{2d}$, -$N(R^{2e})C(O)O(R^{2d})$, -$N(R^{2e})C(O)NR^{2b}R^{2c}$, -$N(R^{2e})S(O)_2NR^{2b}R^{2c}$, –($C_1$-$C_6$ alkylenyl)-G^{2a}, –(C_1-C_6 alkylenyl)-OR^{2a}, -(C_1-C_6 alkylenyl)-$OC(O)R^{2d}$, –(C_1-C_6 alkylenyl)-$OC(O)NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$S(O)_2R^{2d}$, -(C_1-C_6 alkylenyl)-$S(O)_2NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$C(O)R^{2d}$, –(C_1-C_6 alkylenyl)-$C(O)OR^{2a}$, -(C_1-C_6 alkylenyl)-$C(O)NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)R^{2d}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})S(O)_2R^{2d}$, –(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)O(R^{2a})$, –(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)NR^{2b}R^{2c}$, –($C_1$-$C_6$ alkylenyl)-$N(R^{2e})S(O)_2NR^{2b}R^{2c}$, and –($C_1$-$C_6$ alkylenyl)-CN;

R^{2a}, R^{2b}, R^{2c}, and R^{2e}, at each occurrence, are each independently hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, G^{2b}, or C_1-C_6 alkyl wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of –OR^{z1}, $NR^{z1}R^{z2}$, -$C(O)OR^{z1}$, -$C(O)NR^{z1}R^{z2}$, -$S(O)_2R^{z1}$, -$S(O)_2NR^{z1}R^{z2}$, and G^{2b};

R^{2d}, at each occurrence, is independently C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, G^{2b}, or C_1-C_6 alkyl wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of $-OR^{z1}$, $NR^{z1}R^{z2}$, $-C(O)OR^{z1}$, $-C(O)NR^{z1}R^{z2}$, $-S(O)_2R^{z1}$, $-S(O)_2NR^{z1}R^{z2}$, and G^{2b};

R^{z1} and R^{z2}, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

G^{x1}, G^{x2}, G^a, G^b, G^{2a}, and G^{2b}, at each occurrence, are each independently aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl, and each of which is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 of R^v;

L^1 is absent, CH_2, C(O), $(CH_2)_mO$, $(CH_2)_mS(O)_n$ wherein n is 0, 1, or 2; or $(CH_2)_mN(R^z)$ wherein R^z is hydrogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, (C_2-C_3 alkylenyl)-OH, or unsubstituted cyclopropyl;

m is 0 or 1;

G^1 is G^{1a} or -(C_1-C_6 alkylenyl)-G^{1a}; wherein each G^{1a} is independently aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl, and each G^{1a} is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 of R^w;

R^v and R^w, at each occurrence, are each independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, -CN, oxo, $-OR^h$, $-OC(O)R^i$, $-OC(O)NR^jR^k$, $-SR^h$, $-S(O)_2R^h$, $-S(O)_2NR^jR^k$, $-C(O)R^h$, $-C(O)OR^h$, $-C(O)NR^jR^k$, $-NR^jR^k$, $-N(R^h)C(O)R^i$, $-N(R^h)S(O)_2R^i$, $-N(R^h)C(O)O(R^i)$, $-N(R^h)C(O)NR^jR^k$, –(C_1-C_6 alkylenyl)-OR^h, –(C_1-C_6 alkylenyl)-$OC(O)R^i$, -(C_1-C_6 alkylenyl)-$OC(O)NR^jR^k$, –(C_1-C_6 alkylenyl)-$S(O)_2R^h$, –(C_1-C_6 alkylenyl)-$S(O)_2NR^jR^k$, -(C_1-C_6 alkylenyl)-$C(O)R^h$, –(C_1-C_6 alkylenyl)-$C(O)OR^h$, -(C_1-C_6 alkylenyl)-$C(O)NR^jR^k$, –(C_1-C_6 alkylenyl)-NR^jR^k, –(C_1-C_6 alkylenyl)-$N(R^h)C(O)R^i$, -(C_1-C_6 alkylenyl)-$N(R^h)S(O)_2R^i$, –(C_1-C_6 alkylenyl)-$N(R^h)C(O)O(R^i)$, –(C_1-C_6 alkylenyl)-$N(R^h)C(O)NR^jR^k$, or –(C_1-C_6 alkylenyl)-CN;

R^h, R^j, R^k, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

R^i, at each occurrence, is independently C_1-C_6 alkyl or C_1-C_6 haloalkyl.

Compounds of formula (I) may contain one or more asymmetrically substituted atoms. Compounds of formula I may also exist as individual stereoisomers (including enantiomers and diastereomers) and mixtures thereof. Individual stereoisomers of

compounds of formula I may be prepared synthetically from commercially available starting materials that contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution of the individual stereoisomer using methods that are known to those of ordinary skill in the art. Examples of resolution are, for example, (i) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography, followed by liberation of the optically pure product; or (ii) separation of the mixture of enantiomers or diastereomers on chiral chromatographic columns.

Compounds of formula I may also include the various geometric isomers and mixtures thereof resulting from the disposition of substituents around a carbon-carbon double bond, a carbon-nitrogen double bond, a cycloalkyl group, or a heterocycle group. Substituents around a carbon-carbon double bond or a carbon-nitrogen double bond are designated as being of Z or E configuration and substituents around a cycloalkyl or heterocycle are designated as being of cis or trans configuration.

Within the present invention it is to be understood that compounds disclosed herein may exhibit the phenomenon of tautomerism and all tautomeric isomers are included in the scope of the invention.

Thus, the formula drawings within this specification can represent only one of the possible tautomeric, geometric, or stereoisomeric forms. It is to be understood that the invention encompasses any tautomeric, geometric, or stereoisomeric form, and mixtures thereof, and is not to be limited merely to any one tautomeric, geometric, or stereoisomeric form utilized within the formula drawings.

Exemplary compounds of formula (I) include, but are not limited to:

6-methyl-4-(2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-(5-nitro-2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(5-amino-2-phenoxyphenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

2,2,2-trifluoro-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]ethanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]acetamide;

N-methyl-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

ethyl 3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzoate;

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzoic acid;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(pyridin-3-yloxy)phenyl]methanesulfonamide;

6-methyl-4-[2-(morpholin-4-ylmethyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-ethyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxy-N-(tetrahydrofuran-2-ylmethyl)benzamide;

N-cyclopentyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

N-(2,2-difluoroethyl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxy-N-(1,3-thiazol-2-yl)benzamide;

N-(1,1-dioxidotetrahydrothiophen-3-yl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzamide;

4-[5-(hydroxymethyl)-2-phenoxyphenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]ethanesulfonamide;

N,N-dimethyl-N'-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]sulfuric diamide;

N-[5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-phenoxypyridin-3-yl]methanesulfonamide;

N-[3-fluoro-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

N-[4-(2-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[3-chloro-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)phenyl]methanesulfonamide;

6-methyl-4-[2-phenoxy-5-(1H-pyrazol-1-ylmethyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]methanesulfonamide;

N-{3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-[2-(trifluoromethyl)phenoxy]phenyl}methanesulfonamide;

N-[4-(4-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(2-chloro-4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetic acid;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-3,3,3-trifluoropropanamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2,2-dimethylpropanamide;

ethyl 4-(cyclopentylamino)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoate;

4-{5-[(1,1-dioxido-1,2-thiazolidin-2-yl)methyl]-2-phenoxyphenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

BROMODOMAIN INHIBITORS

BACKGROUND

Bromodomains refer to conserved protein structural folds which bind to N-acetylated lysine residues that are found in some proteins. The BET family of bromodomain containing proteins is comprised of four members (BRD2, BRD3, BRD4 and BRDt). Each member of the BET family employs two bromodomains to recognize N-acetylated lysine residues found primarily, but not exclusively, on the amino-terminal tails of histone proteins. These interactions modulate gene expression by recruiting transcription factors to specific genome locations within chromatin. For example, histone-bound BRD4 recruits the transcription factor P-TEFb to promoters, resulting in the expression of a subset of genes involved in cell cycle progression (Yang et al., Mol. Cell. Biol. 28: 967-976 (2008)). BRD2 and BRD3 also function as transcriptional regulators of growth promoting genes (LeRoy et al., Mol. Cell 30: 51-60 (2008)). BET family members were recently established as being important for the maintenance of several cancer types (Zuber et al., Nature 478: 524-528 (2011); Mertz et al; Proc. Nat'l. Acad. Sci. 108: 16669-16674 (2011); Delmore et al., Cell 146: 1-14, (2011); Dawson et al., Nature 478: 529-533 (2011)). BET family members have also been implicated in mediating acute inflammatory responses through the canonical NF-KB pathway (Huang et al., Mol. Cell. Biol. 29: 1375-1387 (2009)) resulting in the upregulation of genes associated with the production of cytokines (Nicodeme et al., Nature 468: 1119-1123, (2010)). In addition, bromodomain function has been implicated in kidney disease (Zhang, et al., J. Biol. Chem. 287: 28840-28851 (2012)). BRD2 function has also been linked to a predisposition for dyslipidemia or improper regulation of adipogenesis, elevated inflammatory profiles and increased susceptibility to autoimmune diseases (Denis, Discovery Medicine 10: 489-499 (2010)). The human immunodeficiency virus utilizes BRD4 to initiate transcription of viral RNA from stably integrated viral DNA (Jang et al., Mol. Cell, 19: 523-534 (2005)). BET bromodomain inhibitors have also been shown to reactivate HIV transcription in models of latent T cell infection and latent monocyte infection (Banerjee, et al, J. Leukocyte Biol. doi:10.1189/jlb.0312165). BRDt has an important role in spermatogenesis (Matzuk, et al., Cell 150: 673-684 (2012)). Accordingly, there is an ongoing medical need to develop new drugs to treat diseases and indications involving bromodomain function, including BET bromodomain function.

4-{[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzyl]amino}-4-oxobutanoic acid;

4-[2-(2,4-difluorophenoxy)-5-(1,1-dioxido-1,2-thiazolidin-2-yl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(benzyloxy)-5-(2-hydroxyethyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

methyl [4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetate;

2-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N-ethylacetamide;

2-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N,N-dimethylacetamide;

N-[4-(3,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]methanesulfonamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(tetrahydrofuran-3-yl)benzamide;

4-{2-(2,4-difluorophenoxy)-5-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(1-methyl-2-oxopyrrolidin-3-yl)benzamide;

tert-butyl {1-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoyl]pyrrolidin-3-yl}carbamate;

4-[2-(2,4-difluorophenoxy)-5-(pyrrolidin-1-ylcarbonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(morpholin-4-ylcarbonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(cyclohexyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(cyclopentyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl}methanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-3-yloxy)phenyl]methanesulfonamide;

6-methyl-4-[2-(morpholin-4-ylcarbonyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]ethanesulfonamide;

N-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2-fluoroethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N'-methylsulfuric diamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]ethanesulfonamide;

methyl 6-methyl-7-oxo-4-(2-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

methyl 1,6-dimethyl-7-oxo-4-(2-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

ethyl 4-(5-amino-2-phenoxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

6-methyl-4-(5-(methylsulfonamido)-2-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid;

ethyl 6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

N-ethyl-6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

ethyl 4-(5-amino-2-phenoxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate;

ethyl 4-[5-(ethylamino)-2-phenoxyphenyl]-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate;

ethyl 4-{5-[ethyl(methylsulfonyl)amino]-2-phenoxyphenyl}-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate;

6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxylic acid;

6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide;

6-methyl-N-[2-(4-methylpiperazin-1-yl)ethyl]-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

N-ethyl-6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide;

6-methyl-4-(2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-d]pyridazin-7-one;

N-ethyl-N,6-dimethyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazine-2-carboxamide;

4-{4-[(ethylsulfonyl)amino]-2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenoxy}benzamide;

6-methyl-4-[5-(methylsulfonyl)-2-phenoxyphenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide;

N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide;

6-methyl-4-(2-phenoxyphenyl)-2-phenyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-{3-[2-(hydroxymethyl)-6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-4-yl]-4-phenoxyphenyl}methanesulfonamide;

N-[4-(4-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

2-fluoro-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]ethanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]propane-1-sulfonamide;

N-[4-(4-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]propane-1-sulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]propane-1-sulfonamide;

3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxybenzenesulfonamide;

6-(cyclohexylamino)-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

6-(cyclohexylamino)-N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

N-methyl-N'-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]sulfuric diamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)phenyl]propane-1-sulfonamide;

2,2,2-trifluoro-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)phenyl]ethanesulfonamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl}ethanesulfonamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl}propane-1-sulfonamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl}-2,2,2-trifluoroethanesulfonamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl}-N'-methylsulfuric diamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-3-yloxy)phenyl]ethanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-3-yloxy)phenyl]propane-1-sulfonamide;

2,2,2-trifluoro-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-3-yloxy)phenyl]ethanesulfonamide;

N-methyl-N'-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-3-yloxy)phenyl]sulfuric diamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-4-yloxy)phenyl]ethanesulfonamide;

N,N-dimethyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide;

5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(phenylamino)pyridine-3-sulfonamide;

N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(phenylamino)pyridine-3-sulfonamide;

N-[4-(4-cyanophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2-fluoroethanesulfonamide;

2-fluoro-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]propane-1-sulfonamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(pyrimidin-2-yl)benzamide;

4-(2,4-difluorophenoxy)-N-(2,6-dimethoxypyridin-3-yl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

4-(2,4-difluorophenoxy)-N-(1H-indazol-6-yl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

4-[2-(2,4-difluorophenoxy)-5-{[4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl]carbonyl}phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(2,4-difluorophenoxy)-N-[4-(dimethylamino)phenyl]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(pyridin-4-ylmethyl)benzamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-[2-(2-oxopyrrolidin-1-yl)ethyl]benzamide;

4-(2,4-difluorophenoxy)-N-(2-hydroxy-2-methylpropyl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

4-(2,4-difluorophenoxy)-N-[2-(5-methoxy-1H-indol-3-yl)ethyl]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

N-(3,4-difluorobenzyl)-4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-[4-(trifluoromethoxy)benzyl]benzamide;

2-{4-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoyl]piperazin-1-yl}-N,N-dimethylacetamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(pyridin-3-ylmethyl)benzamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(pyridin-2-ylmethyl)benzamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(3,4,5-trimethoxybenzyl)benzamide;

4-(2,4-difluorophenoxy)-N-[2-(dimethylamino)ethyl]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

N-[2-(1,3-benzodioxol-5-yl)ethyl]-4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

4-(2,4-difluorophenoxy)-N-[2-(1H-indol-3-yl)ethyl]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide;

4-[2-(2,4-difluorophenoxy)-5-{[4-(furan-2-ylcarbonyl)piperazin-1-yl]carbonyl}phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

tert-butyl {1-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoyl]piperidin-4-yl}carbamate;

tert-butyl 4-{[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzoyl]amino}piperidine-1-carboxylate;

4-[2-(2,4-difluorophenoxy)-5-{[4-(ethylsulfonyl)piperazin-1-yl]carbonyl}phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(4-chlorobenzoyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(4-chlorophenyl)(hydroxy)methyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(pyrimidin-5-yloxy)phenyl]ethanesulfonamide;

N-{3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-[(1-methyl-1H-pyrazol-5-yl)methoxy]phenyl}ethanesulfonamide;

N-{4-[(1,3-dimethyl-1H-pyrazol-5-yl)methoxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl}ethanesulfonamide;

N-[4-(2,2-dimethylpropoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

N-[4-(cyclopropylmethoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

4-[2-(cyclohexylamino)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[5-amino-2-(2,4-difluorophenoxy)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-d]pyridazin-7-one;

4-[2-(2-fluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(3-fluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(4-fluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2-chlorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(3-chlorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(4-chlorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

3-[2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(methylsulfonyl)phenoxy]benzonitrile;

4-[2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(methylsulfonyl)phenoxy]benzonitrile;

6-methyl-4-{5-(methylsulfonyl)-2-[3-(trifluoromethyl)phenoxy]phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclopropylmethoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-4-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-4-yl)phenyl]ethanesulfonamide;

4-[2-(isoquinolin-5-yloxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[5-(methylsulfonyl)-2-(quinolin-6-yloxy)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[2-chloro-5-(trifluoromethyl)phenoxy]-5-(methylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[2-fluoro-5-(trifluoromethyl)phenoxy]-5-(methylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

2-{4-[2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(methylsulfonyl)phenoxy]phenyl}acetamide;

4-[2-(3-aminophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[5-(methylsulfonyl)-2-(tetrahydrofuran-3-ylamino)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(ethylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(4,4-difluorocyclohexyl)oxy]-5-(ethylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{5-(ethylsulfonyl)-2-[(1-methylpiperidin-4-yl)oxy]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,1,3-benzothiadiazol-4-yloxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(isoquinolin-7-yloxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,5-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(3,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{5-(methylsulfonyl)-2-[(1-oxo-2,3-dihydro-1H-inden-4-yl)oxy]phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(3,5-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[2-(4-methylphenoxy)-5-(methylsulfonyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2-methoxyphenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{2-[(2-methylpyridin-3-yl)oxy]-5-(methylsulfonyl)phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[3-(dimethylamino)phenoxy]-5-(methylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{5-(methylsulfonyl)-2-[(1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{5-(methylsulfonyl)-2-[(3-oxo-2,3-dihydro-1H-inden-5-yl)oxy]phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

2-[2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(methylsulfonyl)phenoxy]benzonitrile;

4-[2-(3-chloro-2-fluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[5-(methylsulfonyl)-2-(naphthalen-1-yloxy)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2-fluoro-5-methylphenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(5-fluoro-2-methylphenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[5-(methylsulfonyl)-2-(quinolin-7-yloxy)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(4-chloro-3-fluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[5-(methylsulfonyl)-2-(pyridin-3-yloxy)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,3-dihydro-1H-inden-5-yloxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{5-(methylsulfonyl)-2-[4-(propan-2-yl)phenoxy]phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(isoquinolin-8-yloxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[5-(methylsulfonyl)-2-(3,4,5-trifluorophenoxy)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(2-benzylphenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(biphenyl-2-yl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(1,4-dioxaspiro[4.5]dec-8-yloxy)-5-(ethylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclopropylmethoxy)-5-(ethylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{5-(ethylsulfonyl)-2-[(4-oxocyclohexyl)oxy]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(cyclopropylmethyl)amino]-5-(ethylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{5-(methylsulfonyl)-2-[(tetrahydrofuran-3-ylmethyl)amino]phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{5-(ethylsulfonyl)-2-[(cis-4-hydroxycyclohexyl)oxy]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{5-(ethylsulfonyl)-2-[(trans-4-hydroxycyclohexyl)oxy]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclopropylmethoxy)-5-(ethylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-d]pyridazin-7-one;

6-methyl-4-[5-(methylsulfonyl)-2-(tetrahydrofuran-3-yloxy)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(3-fluorooxetan-3-yl)methoxy]-5-(methylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-(cyclopropylmethoxy)-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

6-(cyclopropylmethoxy)-N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

6-[(cyclopropylmethyl)amino]-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

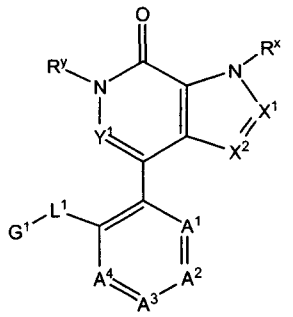
6-[(cyclopropylmethyl)amino]-N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

4-{5-(ethylsulfonyl)-2-[(cis-4-hydroxy-4-methylcyclohexyl)oxy]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{5-(ethylsulfonyl)-2-[(trans-4-hydroxy-4-methylcyclohexyl)oxy]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

SUMMARY

In one aspect the present invention provides for compounds of formula (I) or pharmaceutically acceptable thereof,



(I)

wherein

R^x is hydrogen or C_1-C_3 alkyl;

R^y is C_1-C_3 alkyl, -(C_2-C_3 alkylenyl)-OH, or C_1-C_3 haloalkyl;

X^1 is N or CR^{x1} wherein

R^{x1} is hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -$C(O)OR^{ax1}$, -$C(O)NR^{bx1}R^{cx1}$, -$C(O)R^{dx1}$, $S(O)_2R^{dx1}$, -$S(O)_2NR^{bx1}R^{cx1}$, G^{x1}, C_1-C_6 haloalkyl, or C_1-C_6 alkyl; wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax1}, SR^{ax1}, $S(O)R^{dx1}$, $S(O)_2R^{dx1}$, $NR^{bx1}R^{cx1}$, -$C(O)R^{ax1}$, -$C(O)OR^{ax1}$, -$C(O)NR^{bx1}R^{cx1}$, -$S(O)_2NR^{bx1}R^{cx1}$, and G^{x1};

R^{ax1}, R^{bx1}, and R^{cx1}, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^a, or -(C_1-C_6 alkylenyl)-G^a;

R^{dx1}, at each occurrence, are each independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^a, or -(C_1-C_6 alkylenyl)-G^a;

X^2 is N or CR^{x2}; wherein

R^{x2} is hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -$C(O)OR^{ax2}$, -$C(O)NR^{bx2}R^{cx2}$, -$C(O)R^{dx2}$, -C(O)H, $S(O)_2R^{dx2}$, -$S(O)_2NR^{bx2}R^{cx2}$, G^{x2}, C_1-C_6 haloalkyl, or C_1-C_6 alkyl; wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax2}, SR^{ax2}, $S(O)R^{dx2}$, $S(O)_2R^{dx2}$, $NR^{bx2}R^{cx2}$, -$C(O)R^{ax2}$, -$C(O)OR^{ax2}$, -$C(O)NR^{bx2}R^{cx2}$, -$S(O)_2NR^{bx2}R^{cx2}$, and G^{x2};

R^{ax2}, R^{bx2}, and R^{cx2}, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^b, or -(C_1-C_6 alkylenyl)-G^b;

4-[2-(cyclobutyloxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclopentylmethoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclohexyloxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclopentyloxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[5-(methylsulfonyl)-2-(tetrahydrofuran-3-ylmethoxy)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{5-(methylsulfonyl)-2-[2-(2-oxoimidazolidin-1-yl)ethoxy]phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2-cyclopropylethoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cycloheptyloxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[2-(2-methylpropoxy)-5-(methylsulfonyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[2-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}-5-(methylsulfonyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{2-[(2-methylcyclopropyl)methoxy]-5-(methylsulfonyl)phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclohexylmethoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{2-[2-(1-methylpyrrolidin-2-yl)ethoxy]-5-(methylsulfonyl)phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[5-(methylsulfonyl)-2-{[(2R)-5-oxopyrrolidin-2-yl]methoxy}phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{5-(methylsulfonyl)-2-[2-(morpholin-4-yl)ethoxy]phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-[5-(methylsulfonyl)-2-{[(2S)-5-oxopyrrolidin-2-yl]methoxy}phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(1-tert-butoxypropan-2-yl)oxy]-5-(methylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(1S,4R)-bicyclo[2.2.1]hept-2-ylmethoxy]-5-(methylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{2-[(1-methylcyclopropyl)methoxy]-5-(methylsulfonyl)phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{5-(methylsulfonyl)-2-[2-(2-oxopyrrolidin-1-yl)ethoxy]phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-methyl-4-{2-[(4-methylcyclohexyl)oxy]-5-(methylsulfonyl)phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclobutylmethoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]cyclopropanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2-methoxyethanesulfonamide;

6-methyl-4-{5-(methylsulfonyl)-2-[tricyclo[3.3.1.1^{3,7}]dec-2-yloxy]phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[(cyclopropylmethyl)amino]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

4-[(cyclopropylmethyl)amino]-N-methyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

4-{2-[(2,2-difluorocyclopropyl)methoxy]-5-(ethylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(4-bromo-2-methoxyphenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-(2,4-difluorophenoxy)-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

4-{2-(cyclopropylmethoxy)-5-[(trifluoromethyl)sulfonyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(cyclopropylmethyl)amino]-5-[(trifluoromethyl)sulfonyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-[(cyclopropylmethyl)amino]-N,N-dimethyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

6-(2,4-difluorophenoxy)-N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

4-[2-(cyclopropylmethoxy)-6-methylphenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{5-(ethylsulfonyl)-2-[(cis-4-methoxycyclohexyl)oxy]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(cyclopropylmethoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

4-(cyclopropylmethoxy)-N-methyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

N-[4-(cyclopropylmethoxy)-2-methyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-N-ethyl-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-2-(morpholin-4-ylcarbonyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-2-[(4-methylpiperazin-1-yl)carbonyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-7-oxo-N-(1,3-thiazol-2-yl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

ethyl 4-[2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(methylsulfonyl)phenoxy]piperidine-1-carboxylate;

4-[2-ethoxy-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{5-(ethylsulfonyl)-2-[(trans-4-methoxycyclohexyl)oxy]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(cyclopropylmethyl)amino]-5-(propan-2-ylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(cyclopropylmethoxy)-2-methyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(cyclopropylmethoxy)-2-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

4-[5-(ethylsulfonyl)-2-(tetrahydro-2H-thiopyran-4-yloxy)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxy]-5-(ethylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-(2,4-difluorophenoxy)-N,N-dimethyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

4-[2-(cyclopropylamino)-5-(ethylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(5-(ethylsulfonyl)-2-(cis-4-methoxy-4-methylcyclohexyloxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-N,N,6-trimethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

6-methyl-4-{5-(methylsulfonyl)-2-[4-(methylsulfonyl)phenoxy]phenyl}-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(propan-2-ylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-(cyclopropylmethoxy)-N,N-diethyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

4-(cyclopropylmethoxy)-N,N-dimethyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

4-[2-(cyclopropylmethoxy)-5-fluorophenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(trifluoromethyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-2-(hydroxymethyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,3-dihydro-1H-inden-2-yloxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-2-(1-hydroxyethyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-2-[(dimethylamino)methyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-2-(morpholin-4-ylmethyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-2-[(4-methylpiperazin-1-yl)methyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-2-[(phenylamino)methyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-2-[(1,3-thiazol-2-ylamino)methyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-2-[(tetrahydrofuran-3-ylamino)methyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclopropylmethoxy)-5-(phenylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclopropylmethoxy)-5-(morpholin-4-ylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-(2,4-difluorophenoxy)-5-[(methylsulfonyl)methyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)pyridin-3-yl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-2-[(pyridin-3-yloxy)methyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[5-(cyclopropylsulfonyl)-2-(2,4-difluorophenoxy)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-2-(prop-1-en-2-yl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-2-(phenoxymethyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(morpholin-4-ylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(ethylsulfonyl)pyridin-3-yl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2-(morpholin-4-yl)ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N-[2-(dimethylamino)ethyl]ethanesulfonamide;

4-{2-(2,4-difluorophenoxy)-5-[(ethylsulfonyl)methyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-(2,4-difluorophenoxy)-5-[2-(ethylsulfonyl)propan-2-yl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(pyrrolidin-1-ylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2-(dimethylamino)ethanesulfonamide;

ethyl 4-[4-(ethylsulfonyl)-2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenoxy]piperidine-1-carboxylate;

4-[2-(cyclopropylmethoxy)-5-(pyrrolidin-1-ylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(1-acetylpiperidin-4-yl)oxy]-5-(ethylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[4-(ethylsulfonyl)-2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenoxy]benzonitrile;

4-[2-(cyclopropylmethoxy)-5-(2,3-dihydro-1H-indol-1-ylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-(2,4-difluorophenoxy)-5-[(phenylsulfonyl)methyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(2,2-difluorocyclopropyl)methoxy]-5-(pyrrolidin-1-ylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-(cyclopropylmethoxy)-5-[(3,3-difluoroazetidin-1-yl)sulfonyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[2-(2-hydroxyethyl)phenoxy]-5-(methylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclopropylmethoxy)-5-{[3-(dimethylamino)pyrrolidin-1-yl]sulfonyl}phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-(2,4-difluorophenoxy)-5-[(methylsulfonyl)methyl]pyridin-3-yl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

tert-butyl 4-[4-(ethylsulfonyl)-2-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenoxy]piperidine-1-carboxylate;

4-(cyclopropylmethoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-phenylbenzenesulfonamide;

4-[2-(cyclopropylmethoxy)-5-(pyrrolidin-1-ylmethyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclopropylmethoxy)-5-(pyridin-3-yl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclopropylmethoxy)-5-(morpholin-4-ylmethyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{5-(ethylsulfonyl)-2-[3-(hydroxymethyl)phenoxy]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclopropylmethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(2,3-dihydro-1H-indol-1-ylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin-4-yl)phenyl]ethanesulfonamide;

4-{2-(2,4-difluorophenoxy)-5-[(methylsulfonyl)methyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrazolo[3,4-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(ethylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrazolo[3,4-c]pyridin-7-one;

4-[2-(cyclopropylmethoxy)-5-(ethylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrazolo[3,4-c]pyridin-7-one;

N-[2-cyano-4-(2,4-difluorophenoxy)-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

tert-butyl 4-[4-(cyclopropylmethoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-3,6-dihydropyridine-1(2H)-carboxylate;

4-[5-(6-aminopyridin-3-yl)-2-(cyclopropylmethoxy)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(2,2-difluorocyclopropyl)methoxy]-5-(ethylsulfonyl)phenyl}-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

4-{2-[(cyclopropylmethyl)amino]-5-[(methylsulfonyl)methyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(cyclopropylmethyl)amino]-5-(methylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[5-(ethylsulfonyl)-2-(pyrrolidin-1-yl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[5-(ethylsulfonyl)-2-(4-methylpiperazin-1-yl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(4-fluorophenyl)amino]-5-(methylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(cyclopropylmethoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-N-(pyridin-3-ylmethyl)benzenesulfonamide;

4-[4-(cyclopropylmethoxy)-3'-fluorobiphenyl-3-yl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(4-fluorophenyl)amino]-5-[(methylsulfonyl)methyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

[4-(cyclopropylmethoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]acetonitrile;

N-{4-(2,4-difluorophenoxy)-3-[2-(hydroxymethyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl]phenyl}ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-{6-methyl-2-[(4-methylpiperazin-1-yl)carbonyl]-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl}phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-{6-methyl-2-[(4-methylpiperazin-1-yl)methyl]-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl}phenyl]ethanesulfonamide;

4-[2-(cyclopropylmethoxy)-5-(1,2,3,6-tetrahydropyridin-4-yl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N-(2-methoxyethyl)ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N-(pyridin-2-ylmethyl)ethanesulfonamide;

N-(cyclopropylmethyl)-N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N-[2-(2-oxopyrrolidin-1-yl)ethyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N-(tetrahydrofuran-2-ylmethyl)ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N-(3,3,3-trifluoropropyl)ethanesulfonamide;

4-(cyclopropylmethoxy)-N-(4-fluorophenyl)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

4-[2-(cyclopropylmethoxy)-5-(6-fluoropyridin-3-yl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(2,4-difluorophenoxy)-3-(3-formyl-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

N-{4-(2,4-difluorophenoxy)-3-[6-methyl-3-(morpholin-4-ylmethyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl]phenyl}ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-{6-methyl-3-[(4-methylpiperazin-1-yl)methyl]-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl}phenyl]ethanesulfonamide;

4-{2-[(cyclopropylmethyl)amino]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4'-(cyclopropylmethoxy)-3'-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)biphenyl-3-carbonitrile; and

4-{2-(cyclopropylmethoxy)-5-[(4-hydroxypiperidin-1-yl)sulfonyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one.

In certain embodiments, a compound of formula I is selected from the group consisting of:

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

6-methyl-4-[5-(methylsulfonyl)-2-phenoxyphenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-6-(tetrahydrofuran-3-yloxy)pyridine-3-sulfonamide;

N-[4-(2-chloro-4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]ethanesulfonamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl}methanesulfonamide; and

N-[4-(4-fluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide; or a pharmaceutically acceptable salt thereof.

In certain embodiments, a compound of formula I is selected from the group consisting of:

4-{2-(2,4-difluorophenoxy)-5-[(methylsulfonyl)methyl]pyridin-3-yl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

4-(cyclopropylmethoxy)-N-methyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

4-{2-[(4,4-difluorocyclohexyl)oxy]-5-(ethylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(5-(ethylsulfonyl)-2-(cis-4-methoxy-4-methylcyclohexyloxy)phenyl)-6-methyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one;

6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

4-{2-(2,4-difluorophenoxy)-5-[(methylsulfonyl)methyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(2,4-difluorophenoxy)-5-(ethylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{5-(ethylsulfonyl)-2-[(trans-4-methoxycyclohexyl)oxy]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

R^{dx2}, at each occurrence, is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^b, or -(C_1-C_6 alkylenyl)-G^b;

Y^1 is N or CR^u; wherein R^u is hydrogen, C_1-C_6 alkyl, halogen, or C_1-C_6 haloalkyl;

A^1 is N or CR^1, A^2 is N or CR^2, A^3 is N or CR^3; and A^4 is N or CR^4; with the proviso that zero, one, two, or three of A^1, A^2, A^3, and A^4 are N;

R^1, R^3, and R^4 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, CN, or NO_2;

R^2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, -CN, NO_2, G^{2a}, $-OR^{2a}$, $-OC(O)R^{2d}$, $-OC(O)NR^{2b}R^{2c}$, $-SR^{2a}$, $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)OR^{2a}$, $-C(O)NR^{2b}R^{2c}$, $-NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})C(O)O(R^{2d})$, $-N(R^{2e})C(O)NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, –($C_1$-$C_6$ alkylenyl)-G^{2a}, –(C_1-C_6 alkylenyl)-OR^{2a}, -(C_1-C_6 alkylenyl)-$OC(O)R^{2d}$, –(C_1-C_6 alkylenyl)-$OC(O)NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$S(O)_2R^{2d}$, -(C_1-C_6 alkylenyl)-$S(O)_2NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$C(O)R^{2d}$, –(C_1-C_6 alkylenyl)-$C(O)OR^{2a}$, -(C_1-C_6 alkylenyl)-$C(O)NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)R^{2d}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})S(O)_2R^{2d}$, –(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)O(R^{2a})$, –(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)NR^{2b}R^{2c}$, –($C_1$-$C_6$ alkylenyl)-$N(R^{2e})S(O)_2NR^{2b}R^{2c}$, and –($C_1$-$C_6$ alkylenyl)-CN;

R^{2a}, R^{2b}, R^{2c}, and R^{2e}, at each occurrence, are each independently hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, G^{2b}, or C_1-C_6 alkyl wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of $-OR^{z1}$, $NR^{z1}R^{z2}$, $-C(O)OR^{z1}$, $-C(O)NR^{z1}R^{z2}$, $-S(O)_2R^{z1}$, $-S(O)_2NR^{z1}R^{z2}$, and G^{2b};

R^{2d}, at each occurrence, is independently C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, G^{2b}, or C_1-C_6 alkyl wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of $-OR^{z1}$, $NR^{z1}R^{z2}$, $-C(O)OR^{z1}$, $-C(O)NR^{z1}R^{z2}$, $-S(O)_2R^{z1}$, $-S(O)_2NR^{z1}R^{z2}$, and G^{2b};

R^{z1} and R^{z2}, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

4-{2-[(cyclopropylmethyl)amino]-5-(ethylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[(cyclopropylmethyl)amino]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

4-[2-(cyclopropylmethoxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-[2-(cyclohexyloxy)-5-(methylsulfonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one; and

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]ethanesulfonamide;

or a pharmaceutically acceptable salt thereof.

In certain embodiments, a compound of the present invention is N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide, or a pharmaceutically acceptable salt thereof.

Compounds of formula I can be used in the form of pharmaceutically acceptable salts. The phrase "pharmaceutically acceptable salt" means those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio.

Pharmaceutically acceptable salts have been described in S. M. Berge et al. J. Pharmaceutical Sciences, 1977, 66: 1-19.

Compounds of formula (I) may contain either a basic or an acidic functionality, or both, and can be converted to a pharmaceutically acceptable salt, when desired, by using a suitable acid or base. The salts may be prepared in situ during the final isolation and purification of the compounds of the invention.

Examples of acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, malate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate,

bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as, but not limited to, methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as, but not limited to, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid and such organic acids as acetic acid, fumaric acid, maleic acid, 4-methylbenzenesulfonic acid, succinic acid and citric acid.

Basic addition salts may be prepared in situ during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as, but not limited to, the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as, but not limited to, lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other examples of organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

The term "pharmaceutically acceptable prodrug" or "prodrug"as used herein, represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use.

The present invention contemplates compounds of formula (I) formed by synthetic means or formed by in vivo biotransformation of a prodrug.

Compounds described herein can exist in unsolvated as well as solvated forms, including hydrated forms, such as hemi-hydrates. In general, the solvated forms, with pharmaceutically acceptable solvents such as water and ethanol among others are equivalent to the unsolvated forms for the purposes of the invention.

General Synthesis

The compounds described herein, including compounds of general formula (I) and specific examples, may be prepared, for example, through the reaction routes depicted in schemes 1-5. The variables A^1, A^2, A^3, A^4, X^1, X^2, Y^1, L^1, G^1, R^x, and R^y used in the following schemes have the meanings as set forth in the summary and detailed description sections unless otherwise noted.

Abbreviations used in the descriptions of the schemes and the specific examples have the following meanings: n-BuLi or BuLi for n-butyl lithium, DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene, DIAD for diisopropyl azodicarboxylate; DME for 1,2-dimethoxyethane, DMF for dimethylformamide, DMSO for dimethyl sulfoxide, EtOAc for ethyl acetate; mCPBA for 3-chloroperbenzoic acid, MeOH for methanol; $Pd(PPh_3)_4$ for tetrakis(triphenylphosphine)palladium(0), Preparative HPLC for preparative HPLC; THF for tetrahydrofuran, TFA for trifluoroacetic acid, and HPLC for high performance liquid chromatography.

Compounds of general formula (I) may be prepared (a) by treating an aryl halide, an aryl mesylate, or an aryl triflate with an aryl boronic acid or derivatives thereof (e.g. boronic esters) under Suzuki coupling condition (N. Miyama and A. Suzuki, Chem. Rev. 1995, 95:2457-2483, J. Organomet. Chem. 1999, 576:147-148), and (b) removal of the protecting group (PG), as illustrated in Scheme 1. Thus coupling of compounds of formula (1) wherein R^{101} is Br, Cl, mesylate, or triflate with compounds of formula (2) wherein R^{102} is boronic acid or derivatives thereof (e.g. boronic esters), or coupling of (1) wherein R^{101} is boronic acid or derivatives thereof (e.g. boronic esters) with compounds (2) wherein R^{102} is Br, Cl, mesylate, or triflate, provides intermediates of formula (3). Generally, the coupling reaction is effected in the presence of a palladium catalyst and a base, and optionally in the presence of a ligand, and in a suitable solvent at elevated temperature (for example, at about 80 °C to about 150 °C). The reaction may be facilitated by microwave irradiation. Examples of the palladium catalyst include, but are not limited to, tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0), and palladium(II)acetate. Examples of suitable bases that may be employed include, but are not limited to, carbonates or phosphates of sodium, potassium, and cesium; and cesium fluoride. Examples of suitable ligands include, but are not limited to, 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamante, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-phos), and 1,1'- bis(diphenylphosphanyl) ferrocene. Non-limiting examples of suitable solvent include methanol, dimethoxyethane, N,N-

dimethylformamide, dimethylsulfoxide, dioxane, tetrahydropyran, and water, or a mixture thereof.

Alternatively, treatment of formula (1) wherein R^{101} is Br, Cl, or triflate with boronic acid of formula (4), followed by displacement of the fluoride atom in (4) with an appropriate alcohol or amine of formula G^1-L^1-H wherein L^1 is O or NH, provides compounds of formula (3) or formula (I) wherein R^x is hydrogen.

Displacement of the fluorine with an alcohol or amine may be achieved in a solvent such as, but not limited to, dimethylsulfoxide, dimethylformamide, dioxane, or tetrahydrofuran, and in the presence of a base such as, but not limited to, cesium carbonate, potassium carbonate, or sodium hydride and at a temperature from about 40°C to about 120 °C.

The protecting group (PG) may be removed in situ during the displacement reaction or the coupling conditions described above.

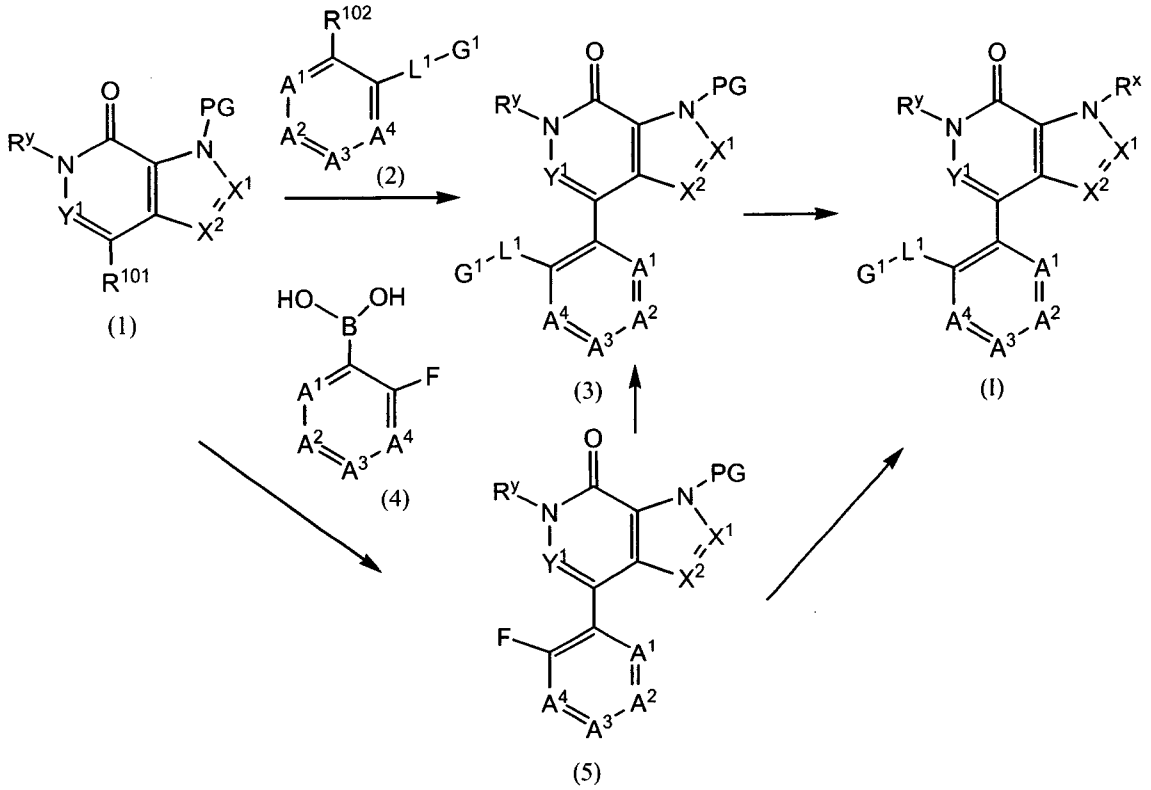
Alternatively, removal of the protecting group (PG) to afford compounds of general formula (I) wherein R^x is hydrogen can be accomplished using reaction conditions known generally to one skilled in the art, or modifications thereof. For example, the tosyl protecting group can be removed in the presence of a base such as, but not limited to, cesium carbonate, sodium hydroxide, or sodium hydride. The reaction is generally performed in the presence of a suitable solvent such as, but not limited to, dimethylsulfoxide, methanol, or tetrahydrofuran, and at a temperature of about 40 °C to about 120 °C. The benzyl protecting group may be removed by hydrogenation in the presence of a catalyst such as, but not limited to, palladium on carbon and under hydrogen atmosphere. The reaction is typically performed in the presence of a solvent such as, but not limited to, methanol or ethyl acetate, and at about room temperature.

Removal of the (trimethylsilyl)ethoxy)methyl protecting group can be achieved by treatment with a base such as, but not limited to, cesium carbonate or sodium hydride, or with a fluoride reagent such as, but not limited to, TBAF (tetrabutylammonium fluoride). The reaction is generally performed in the presence of a suitable solvent such as, but not limited to, dimethylsulfoxide, ethanol, or tetrahydrofuran, and at a temperature of about 40 °C to about 120 °C. Removal of the (trimethylsilyl)ethoxy)methyl protecting group can also be achieved by treatment with an mild acid such as but not limited to, aqueous hydrochloric acid. The reaction is generally performed in the presence of a suitable

solvent such as, but not limited to, ethanol, or methanol, and at a temperature of about 25 °C to about 80 °C.

Conversion of compounds of formula (I) wherein R^x is hydrogen to (I) wherein R^x is C_1-C_3 alkyl can be achieved with an alkylating agent of formula R^xR^{103} wherein R^{103} is halogen, triflate, or mesylate. Generally, the reaction may be conducted in the presence of a base such as, but not limited to, sodium hyride or potassium carbonate, and in a solvent such as, but not limited to, tetrhydrofuran or dimethylformamide, and at a temperature of about 40 °C to about 120 °C.

Scheme 1



Compounds of formula (1) wherein Y^1 is CR^u, X^1 and X^2 are CH, and R^u is hydrogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl may be prepared by general synthetic methods as shown in Scheme 2.

Treatment of compounds of formula (6) wherein halo is Br, Cl, or I, with 1,1-dimethoxy-N,N-dimethylmethanamine at elevated temperature (e.g. about 60 °C to about 100 °C), in the absence or presence of a base, and in a solvent such as, but not limited to, DMF, provide compounds of formula (7). Examples of suitable bases include, but not limited to, lithium or sodium methanolate. Catalytic hydrogenation of (7) in the presence of a catalyst such as, but not limited to, Raney-Nickel and under hydrogen atmosphere (about 30 psi) and in a solvent such as, but not limited to, ethyl acetate, at about room

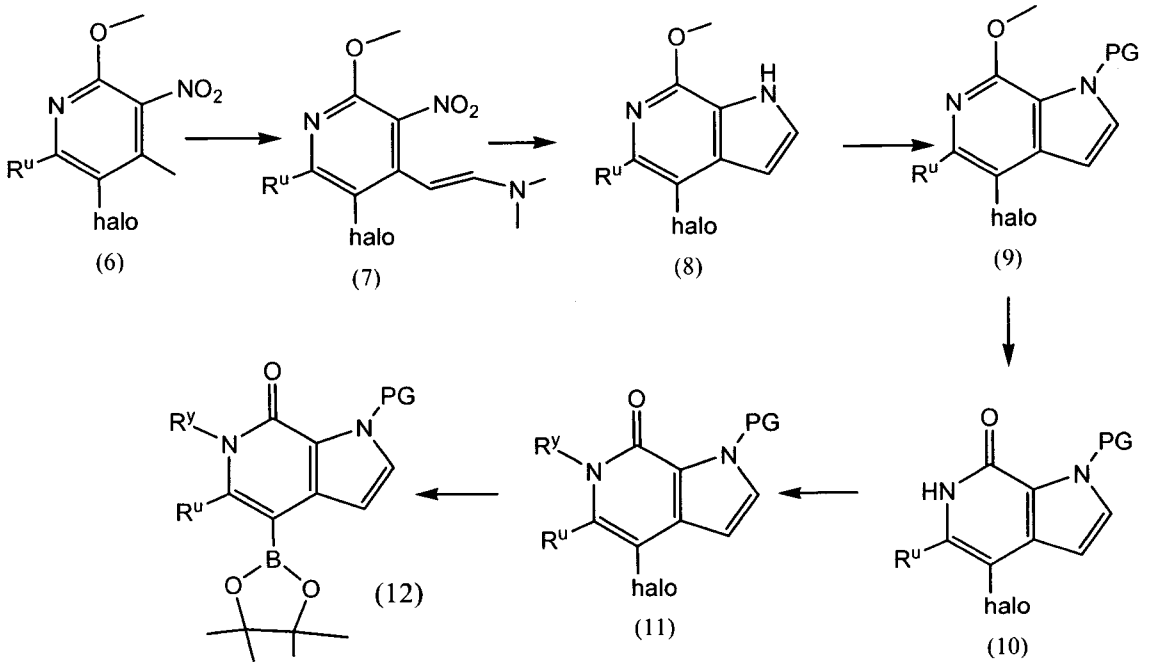
temperature generally affords compounds of formula (8). Protection of the nitrogen atom with protecting group such as, but not limited to, benzyl, tosyl, and (trimethylsilyl)ethoxy)methyl group can be derived from reaction with an appropriate halide in the presence of a strong base such as, but not limited to, sodium hydride, to provide compounds of formula (9).

Treatment of (9) with an acid such as, but not limited to, hydrochloric acid or hydrobromic acid and in a solvent such as, but not limited to, dioxane or water, at about 40 °C to about 100 °C, typically provides compounds of formula (10).

Alkylation of (10) with a halide or mesylate, in the presence of a base such as, but not limited to, sodium hydride, cesium carbonate, or potassium carbonate, and in a solvent such as, but not limited to, dimethylformamide or dimethylsulfoxide at a temperature of about 0 °C to about 50 °C typically provides compounds of formula (11).

Treatment of the compounds of formula (11) with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) generally affords compounds of formula (12). In general, the conversion may be facilitated by a palladium catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0), or palladium(II)acetate, an optional ligand such as, but not limited to, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-phos), or1,1'- bis(diphenylphosphanyl) ferrocene, and a base such as, but not limited to, carbonates, acetates, or phosphates.of sodium, potassium, and cesium; and cesium fluoride. Non-limiting examples of suitable solvents include methanol, dimethoxyethane, N,N-dimethylformamide, dimethylsulfoxide, dioxane, tetrahydropyran, and water, or a mixture thereof.

Scheme 2



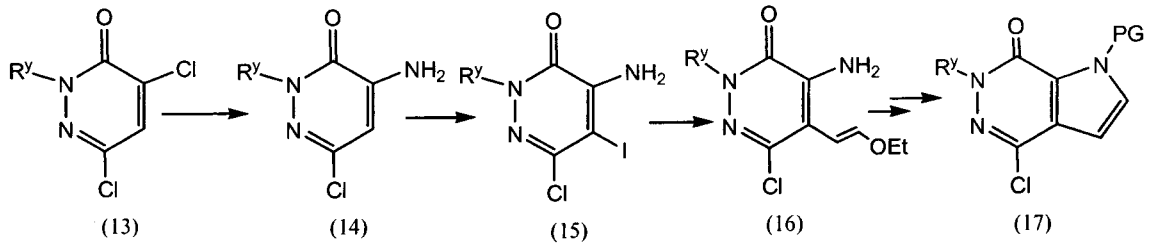
An approach to prepare compounds of formula (1) wherein Y^1 is N, R^{101} is Cl, and X^1 and X^2 are CH, is outlined in Scheme 3.

Treatment of (13) with ammonium hydroxide at about 100 °C to about 150 °C can afford amines of formula (14).

Iodination of (14) with N-iodosuccinimide in a solvent such as, but not limited to, acetonitrile or acetone, at a temperature of about 40 °C to about 85 °C, typically yields compounds of formula (15). Subsequent coupling with (E)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane utilizing Suzuki coupling reaction conditions as described in Scheme 1 provides compounds of formula (16). Cyclization of (16) followed by protection of the nitrogen atom typically affords compounds of formula (17).

Cyclization of (16) may be accomplished in the presence of an acid such as, but not limited to, acetic acid or hydrochloric acid and at an elevated temperature (e.g. about 50 °C to about 100 °C).

Scheme 3



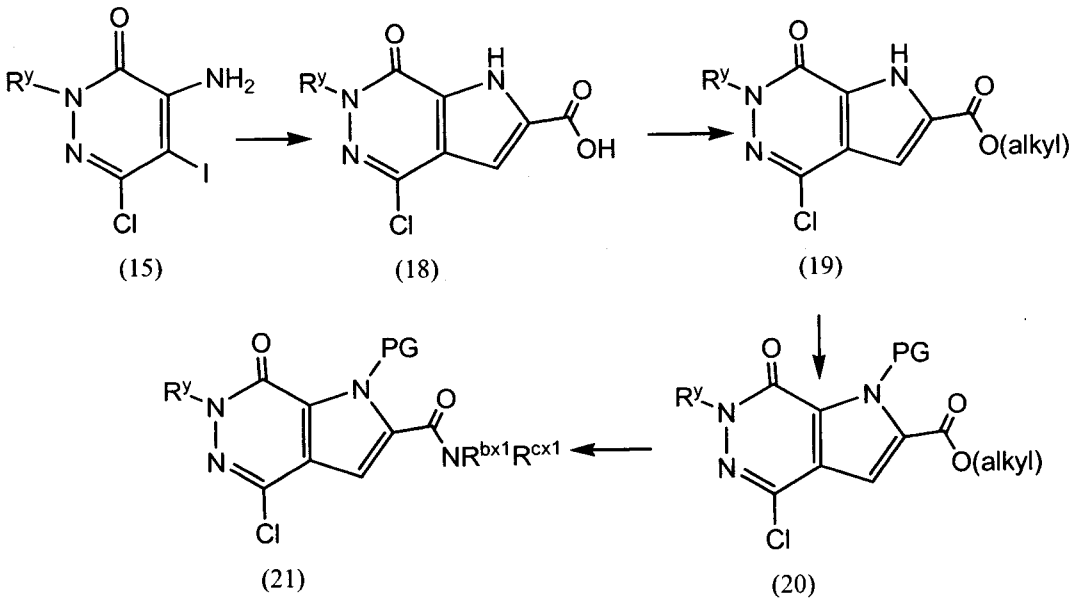
Compounds of formula (1) wherein Y^1 is N, R^{101} is Cl, X^1 is $-COOR^{ax1}$ or $-C(O)NR^{bx1}R^{cx1}$, R^{ax1}, R^{bx1}, and R^{cx1} are hydrogen or C_1-C_6 alkyl, and X^2 is CH may be prepared using the synthetic route exemplified in Scheme 4.

Treatment of (15) with pyruvic acid in the presence of a palladium catalyst such as, but not limited to, palladium(II)acetate, and a base such as, but not limited to, DBU, and in a solvent such as, but not limited to, DMF and at elevated temperature (e.g. at about 80 °C to about 150 °C) generally results in acids of formula (18). Esterification of (18) to (19) may be accomplished by reaction conditions known to one skilled in the art, for example, by treatment with an alcohol under acidic condition. Subsequent protection of (19) using reaction conditions described in Scheme 2 for the conversion of (8) to (9) can provide for compounds of formula (20). Transformation of (20) to (21) may be accomplished by step-wise reaction of (a) hydrolysis of the ester to the corresponding acid and (b) conversion of the acid to the corresponding amides.

The acid can be transformed to the appropriate acid chloride by treatement with oxalyl chloride in the presence of catalytic amount of DMF at about room temperature, and in a suitable solvent such as, but not limited to, tetrahydrofuran or dichloromethane.

The resulting acid chloride may be converted to amides of formula (21) by treatment with an amine of formula $HNR^{bx1}R^{cx1}$ in a solvent such as, but not limited to, tetrahydrofuran, dimethylformamide, or dichloromethane at a temperature from about room temperature to about 50 °C, optionally in the presence of a base such as, but not limited to, triethylamine, diisopropylethylamine, or potassium carbonate, and optionally in the presence of a catalyst such as 4-dimethylaminopyridine. Alternatively, the acid can be reacted with the amine of formula $HNR^{bx1}R^{cx1}$ in a solvent such as, but not limited to, tetrahydrofuran or dimethylformamide in the presence of a coupling reagent such as 1,1'-carbonyldiimidazole (CDI), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl), 1,3-dicyclohexylcarbodiimide (DCC), polymer supported 1,3-dicyclohexylcarbodiimide (PS-DCC), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), in the presence or absence of a coupling auxiliary such as, but not limited to, 1-hydroxy-7-azabenzotriazole (HOAT) or 1-hydroxybenzotriazole hydrate (HOBT). The reaction may be generally conducted in the presence or absence of a base such as, but not limited to, N-methyl morpholine, triethylamine, or diisopropylethylamine.

Scheme 4

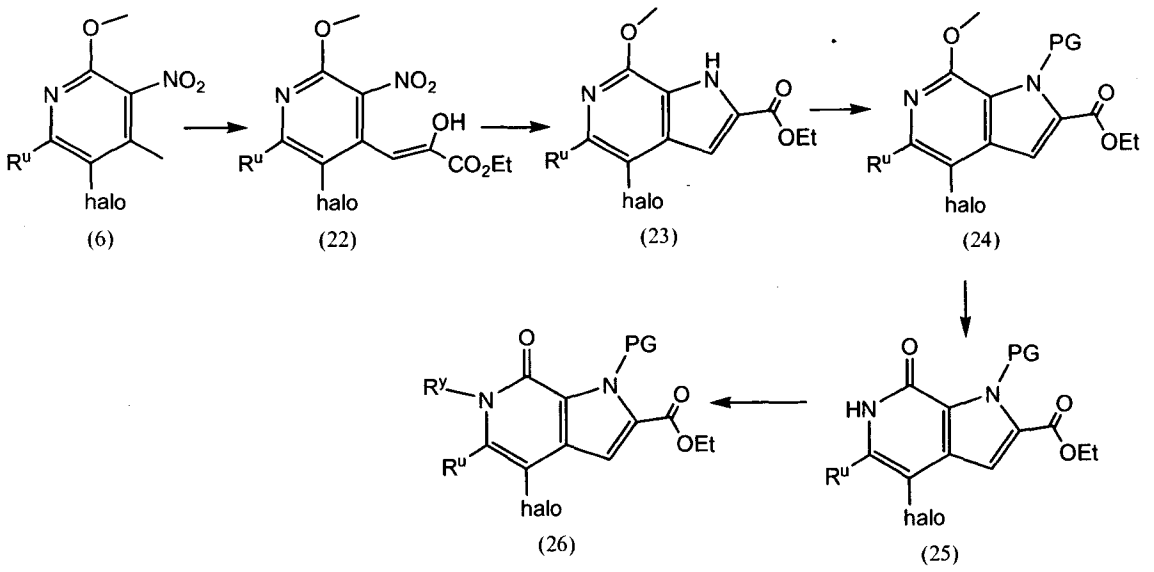


Scheme 5 demonstrates a general approach to the preparation of compounds of formula (1) wherein Y^1 is CR^u, R^{101} is halogen, X^1 is $-COOR^{ax1}$ or $-C(O)NR^{bx1}R^{cx1}$, R^{ax1}, R^{bx1}, and R^{cx1} are hydrogen or C_1-C_6 alkyl, and X^2 is CH.

An ester of formula (23) may be obtained from (a) treatment of (6) with diethyl oxalate in the presence of a base such as, but not limited to, potassium ethoxide or sodium ethoxide, in a solvent such as, but not limited to, potassium ethoxide or sodium ethoxide, in a solvent such as, but not limited to, ethanol, dioxane, or diethyl ether, and at a temperature of about 40 °C to about 80 °C; and (b) cyclization of the resulting (22) in the presence of iron and in ethanol and acetic acid, at a temperature of about 80 °C to about 100 °C. Conversion of (23) to (26) can be achieved by employing reaction conditions discussed above.

An ethyl ester of formula (26) may subsequently be hydrolysed to the corresponding acids. The resulting acids may be transformed to an appropriate ester or amide as described in Scheme 4.

Scheme 5



Optimum reaction conditions and reaction times for each individual step may vary depending on the particular reactants employed and substituents present in the reactants used. Unless otherwise specified, solvents, temperatures and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Reactions may be further processed in the conventional manner, e.g. by eliminating the solvent from the residue and further purified according to methodologies generally known in the art such as, but not limited to, crystallization, distillation, extraction, trituration and chromatography. Unless otherwise described, the starting materials and reagents are either commercially available or may be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature.

Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that may not be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the method are included in the scope of the invention. Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, Protecting Groups in Chemical Synthesis (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. Synthesis of the compounds of the invention may be accomplished by methods analogous to those described in the synthetic schemes described hereinabove and in specific examples.

Starting materials, if not commercially available, may be prepared by procedures

G^{x1}, G^{x2}, G^a, G^b, G^{2a}, and G^{2b}, at each occurrence, are each independently aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl, and each of which is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 of R^v;

L^1 is absent, CH_2, C(O), C(H)(OH), $(CH_2)_mO$, $(CH_2)_mS(O)_n$ wherein n is 0, 1, or 2; or $(CH_2)_mN(R^z)$ wherein R^z is hydrogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, (C_2-C_3 alkylenyl)-OH, or unsubstituted cyclopropyl;

m is 0 or 1;

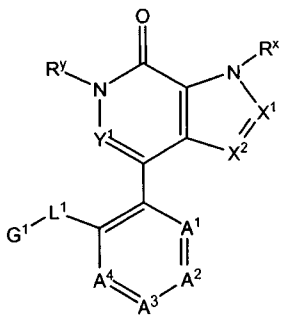
G^1 is C_1-C_6 alkyl, alkoxyalkyl, G^{1a} or -(C_1-C_6 alkylenyl)-G^{1a}; wherein each G^{1a} is independently aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl, and each G^{1a} is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 of R^w;

R^v and R^w, at each occurrence, are each independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, -CN, oxo, $-OR^h$, $-OC(O)R^i$, $-OC(O)NR^jR^k$, $-SR^h$, $-S(O)_2R^h$, $-S(O)_2NR^jR^k$, $-C(O)R^h$, -C(O)-monocyclic heterocycle, -C(O)-monocyclic heteroaryl,$-C(O)OR^h$, $-C(O)NR^jR^k$, $-NR^jR^k$, $-N(R^h)C(O)R^i$, $-N(R^h)S(O)_2R^i$, $-N(R^h)C(O)O(R^i)$, $-N(R^h)C(O)NR^jR^k$, –(C_1-C_6 alkylenyl)-OR^h, –(C_1-C_6 alkylenyl)-$OC(O)R^i$, -(C_1-C_6 alkylenyl)-$OC(O)NR^jR^k$, –(C_1-C_6 alkylenyl)-$S(O)_2R^h$, –(C_1-C_6 alkylenyl)-$S(O)_2NR^jR^k$, -(C_1-C_6 alkylenyl)-$C(O)R^h$, –(C_1-C_6 alkylenyl)-$C(O)OR^h$, -(C_1-C_6 alkylenyl)-$C(O)NR^jR^k$, –(C_1-C_6 alkylenyl)-NR^jR^k, –(C_1-C_6 alkylenyl)-$N(R^h)C(O)R^i$, -(C_1-C_6 alkylenyl)-$N(R^h)S(O)_2R^i$, –(C_1-C_6 alkylenyl)-$N(R^h)C(O)O(R^i)$, –(C_1-C_6 alkylenyl)-$N(R^h)C(O)NR^jR^k$, or –(C_1-C_6 alkylenyl)-CN;

R^h, R^j, R^k, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, or C_1-C_6 haloalkyl; and

R^i, at each occurrence, is independently C_1-C_6 alkyl or C_1-C_6 haloalkyl.

In one aspect the present invention provides for compounds of formula (I) or pharmaceutically acceptable thereof,



selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analogous to the above described schemes or the procedures described in the synthetic examples section.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

Similarly, when a pure geometric isomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

Pharmaceutical Compositions

This invention also provides for pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier, diluent, or excipient therefor. The phrase "pharmaceutical composition" refers to a composition suitable for administration in medical or veterinary use.

The pharmaceutical compositions that comprise a compound of formula (I), alone or or in combination with a second active pharmaceutical agent, may be administered to the subjects orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), bucally or as an oral or nasal spray. The term "parenterally" as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The term "pharmaceutically acceptable carrier" as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellulose

and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such a propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

Pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), vegetable oils (such as olive oil), injectable organic esters (such as ethyl oleate) and suitable mixtures thereof. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

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

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

Alternatively, delayed absorption of a parenterally-administered drug form may be accomplished by dissolving or suspending the drug in an oil vehicle.

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

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

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In certain embodiments, solid dosage forms may contain from 1% to 95% (w/w) of a compound of formula I. In certain embodiments, the compound of formula I may be present in the solid dosage form in a range of from 5% to 70% (w/w). In such solid dosage forms, the active compound may be mixed with at least one inert, pharmaceutically acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

The pharmaceutical composition may be a unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself,

or it can be the appropriate number of any of these in packaged form. The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1000 mg, from 1 mg to 100 mg, or from 1% to 95% (w/w) of a unit dose, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

The dose to be administered to a subject may be determined by the efficacy of the particular compound employed and the condition of the subject, as well as the body weight or surface area of the subject to be treated. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular compound in a particular subject. In determining the effective amount of the compound to be administered in the treatment or prophylaxis of the disorder being treated, the physician can evaluate factors such as the circulating plasma levels of the compound, compound toxicities, and/or the progression of the disease, etc. In general, the dose equivalent of a compound is from about 1 μg/kg to 100 mg/kg for a typical subject.

For administration, compounds of the formula I can be administered at a rate determined by factors that can include, but are not limited to, the LD_{50} of the compound, the pharmacokinetic profile of the compound, contraindicated drugs, and the side-effects of the compound at various concentrations, as applied to the mass and overall health of the subject. Administration can be accomplished via single or divided doses.

The compounds utilized in the pharmaceutical method of the invention can be administered at the initial dosage of about 0.001 mg/kg to about 100 mg/kg daily. In certain embodiments, the daily dose range is from about 0.1 mg/kg to about 10 mg/kg. The dosages, however, may be varied depending upon the requirements of the subject, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Treatment may be initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such carriers as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings and other coatings well-known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned carriers.

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

Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth and mixtures thereof.

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

Compounds of formula I may also be administered in the form of liposomes. Liposomes generally may be derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions

in liposome form may contain, in addition to a compound of formula (I), stabilizers, preservatives, excipients and the like. Examples of lipids include, but are not limited to, natural and synthetic phospholipids and phosphatidyl cholines (lecithins), used separately or together.

Methods to form liposomes have been described, see example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (l976), p. 33 et seq.

Dosage forms for topical administration of a compound described herein include powders, sprays, ointments and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which may be required. Opthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Methods of Use

The compounds of formula I, or pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, can be administered to a subject suffering from a bromodomain-mediated disorder or condition. The term "administering" refers to the method of contacting a compound with a subject. Thus, the compounds of formula I can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, parentally, or intraperitoneally. Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of formula I can be administered transdermally, topically, via implantation, transdermally, topically, and via implantation. In certain embodiments, the compounds of the formula I may be delivered orally. The compounds can also be delivered rectally, bucally, intravaginally, ocularly, andially, or by insufflation. Bromodomain-mediated disorders and conditions can be treated prophylactically, acutely, and chronically using compounds of formula I, depending on the nature of the disorder or condition. Typically, the host or subject in each of these methods is human, although other mammals can also benefit from the administration of a compound of formula I.

A "bromodomain-mediated disorder or condition" is characterized by the participation of one or more bromodomains (e.g., BRD4) in the inception, manifestation of one or more symptoms or disease markers, severity, or progression of a disorder or condition.

Accordingly, compounds of formula I may be used to treat cancer, including, but not limited to acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenström's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

Further, compounds of formula I may be used to treat inflammatory diseases, inflammatory conditions, and autoimmune diseases, including, but not limited to: Addison's disease, acute gout, ankylosing spondylitis, asthma, atherosclerosis, Behcet's disease, bullous skin diseases, chronic obstructive pulmonary disease (COPD), Crohn's disease,dermatitis, eczema,giant cell arteritis, glomerulonephritis, hepatitis, hypophysitis,

inflammatory bowel disease, Kawasaki disease, lupus nephritis, multiple sclerosis, myocarditis,myositis, nephritis, organ transplant rejection, osteoarthritis, pancreatitis, pericarditis, Polyarteritis nodosa, pneumonitis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleritis, sclerosing cholangitis, sepsis, systemic lupus erythematosus, Takayasu's Arteritis, toxic shock, thyroiditis, type I diabetes, ulcerative colitis, uveitis, vitiligo, vasculitis, and Wegener's granulomatosis.

Compounds of formula I, or pharmaceutically acceptable salts thereof, may be used to treat AIDS.

Compounds of formula I, or pharmaceutically acceptable salts thereof, may be used to treat chronic kidney disease or condition including, but are not limited to: diabetic nephropathy, hypertensive nephropathy, HIV-associated nephropathy, glomerulonephritis, lupus nephritis, IgA nephropathy, focal segmental glomerulosclerosis, membranous glomerulonephritis, minimal change disease, polycystic kidney disease and tubular interstitial nephritis.

Compounds of formula I, or pharmaceutically acceptable salts thereof, may be used to treat acute kidney injury or disease or condition including, but are not limited to: ischemia-reperfusion induced, cardiac and major surgery induced, percutaneous coronary intervention induced, radio-contrast agent induced, sepsis induced, pneumonia induced, and drug toxicity induced.

Compounds of formula I, or pharmaceutically acceptable salts thereof, may be used to treat obesity, dyslipidemia, hypercholesterolemia, Alzheimer's disease, metabolic syndrome, hepatic steatosis, type II diabetes, insulin resistance, diabetic retinopathy or diabetic neuropathy.

Compounds of formula I, or pharmaceutically acceptable salts thereof, may be used to provide for male contraception in a male subject comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a male subject in need thereof.

The compounds of formula I can be co-administered to a subject. The term "co-administered" means the administration of two or more different pharmaceutical agents or treatments (e.g., radiation treatment) that are administered to a subject by combination in the same pharmaceutical composition or separate pharmaceutical compositions. Thus co-administration involves administration at the same time of a single pharmaceutical composition comprising two or more pharmaceutical agents or administration of two or more different compositions to the same subject at the same or different times.

The compounds of the invention can be co-administered with a therapeutically effective amount of one or more agents to treat a cancer, where examples of the agents include, such as radiation, alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, apoptosis promoters (for example, Bcl-xL, Bcl-w and Bfl-1) inhibitors, activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs (dual variable domain antibodies), leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNA's, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (bromodomain) inhibitors, proteosome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, etinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, and the like, and in combination with one or more of these agents.

BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding the two cells. The T-cell then attacks the target cancer cell. Examples of BiTE antibodies include adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) and the like. Without being limited by theory, one of the mechanisms by which T-cells elicit apoptosis of the target cancer cell is by exocytosis of cytolytic granule components, which include perforin and granzyme B. In this regard, Bcl-2 has been shown to attenuate the induction of apoptosis by both perforin and granzyme B. These data suggest that inhibition of Bcl-2 could enhance the cytotoxic effects elicited by T-cells when targeted to cancer cells (V.R. Sutton, D.L. Vaux and J.A. Trapani, *J. of Immunology* **1997**, 158 (12), 5783).

SiRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but rather impart increased stability and/or increased cellular potency. Examples of chemical modifications include phosphorothioate groups, 2'-deoxynucleotide, 2'-OCH_3-containing ribonucleotides, 2'-F-

ribonucleotides, 2'-methoxyethyl ribonucleotides, combinations thereof and the like. The siRNA can have varying lengths (e.g., 10-200 bps) and structures (e.g., hairpins, single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1-2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5'- and/ or the 3'-ends of a given strand.

Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally occurring antibodies. The term "multispecific binding protein" means a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins are tetravalent or multivalent binding proteins binding proteins comprising two or more antigen binding sites. Such DVDs may be monospecific (i.e., capable of binding one antigen) or multispecific (i.e., capable of binding two or more antigens). DVD binding proteins comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides are referred to as DVD Ig's. Each half of a DVD Ig comprises a heavy chain DVD polypeptide, a light chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site. Multispecific DVDs include DVD binding proteins that bind DLL4 and VEGF, or C-met and EFGR or ErbB3 and EGFR.

Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, bendamustine, brostallicin, busulfan, carboquone, carmustine (BCNU), chlorambucil, CLORETAZINE® (laromustine, VNP 40101M), cyclophosphamide, decarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine (CCNU), mafosfamide, melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide, ranimustine, temozolomide, thiotepa, TREANDA® (bendamustine), treosulfan, rofosfamide and the like.

Angiogenesis inhibitors include endothelial-specific receptor tyrosine kinase (Tie-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, insulin growth factor-2 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs, vascular endothelial growth factor receptor

(I)

wherein

R^x is hydrogen or C_1-C_3 alkyl;

R^y is C_1-C_3 alkyl, -(C_2-C_3 alkylenyl)-OH, or C_1-C_3 haloalkyl;

X^1 is N or CR^{x1} wherein

R^{x1} is hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, $-C(O)R^{dx1}$, $S(O)_2R^{dx1}$, $-S(O)_2NR^{bx1}R^{cx1}$, G^{x1}, C_1-C_6 haloalkyl, or C_1-C_6 alkyl; wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax1}, SR^{ax1}, $S(O)R^{dx1}$, $S(O)_2R^{dx1}$, $NR^{bx1}R^{cx1}$, $-C(O)R^{ax1}$, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, $-S(O)_2NR^{bx1}R^{cx1}$, and G^{x1};

R^{ax1}, R^{bx1}, and R^{cx1}, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^a, or -(C_1-C_6 alkylenyl)-G^a;

R^{dx1}, at each occurrence, are each independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^a, or -(C_1-C_6 alkylenyl)-G^a;

X^2 is N or CR^{x2}; wherein

R^{x2} is hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-C(O)OR^{ax2}$, $-C(O)NR^{bx2}R^{cx2}$, $-C(O)R^{dx2}$, $S(O)_2R^{dx2}$, $-S(O)_2NR^{bx2}R^{cx2}$, G^{x2}, C_1-C_6 haloalkyl, or C_1-C_6 alkyl; wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax2}, SR^{ax2}, $S(O)R^{dx2}$, $S(O)_2R^{dx2}$, $NR^{bx2}R^{cx2}$, $-C(O)R^{ax2}$, $-C(O)OR^{ax2}$, $-C(O)NR^{bx2}R^{cx2}$, $-S(O)_2NR^{bx2}R^{cx2}$, and G^{x2};

R^{ax2}, R^{bx2}, and R^{cx2}, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^b, or -(C_1-C_6 alkylenyl)-G^b;

R^{dx2}, at each occurrence, is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^b, or -(C_1-C_6 alkylenyl)-G^b;

Y^1 is N or CR^u; wherein R^u is hydrogen, C_1-C_6 alkyl, halogen, or C_1-C_6 haloalkyl;

A^1 is N or CR^1, A^2 is N or CR^2, A^3 is N or CR^3; and A^4 is N or CR^4; with the proviso that zero, one, two, or three of A^1, A^2, A^3, and A^4 are N;

R^1, R^3, and R^4 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, CN, or NO_2;

R^2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, -CN, NO_2, G^{2a}, $-OR^{2a}$, $-OC(O)R^{2d}$, $-OC(O)NR^{2b}R^{2c}$, $-SR^{2a}$, $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)OR^{2a}$, $-C(O)NR^{2b}R^{2c}$, $-NR^{2b}R^{2c}$,

tyrosine kinase (VEGFR) inhibitors and the like.

Antimetabolites include ALIMTA® (pemetrexed disodium, LY231514, MTA), 5-azacitidine, XELODA® (capecitabine), carmofur, LEUSTAT® (cladribine), clofarabine, cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR (5-ethynyl-1-β -D-ribofuranosylimidazole-4-carboxamide), enocitabine, ethnylcytidine, fludarabine, 5-fluorouracil alone or in combination with leucovorin, GEMZAR® (gemcitabine), hydroxyurea, ALKERAN®(melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, nelarabine, nolatrexed, ocfosfate, pelitrexol, pentostatin, raltitrexed, Ribavirin, triapine, trimetrexate, S-1, tiazofurin, tegafur, TS-1, vidarabine, UFT and the like.

Antivirals include ritonavir, hydroxychloroquine and the like.

Aurora kinase inhibitors include ABT-348, AZD-1152, MLN-8054, VX-680, Aurora A-specific kinase inhibitors, Aurora B-specific kinase inhibitors and pan-Aurora kinase inhibitors and the like.

Bcl-2 protein inhibitors include AT-101 ((-)gossypol), GENASENSE® (G3139 or oblimersen (Bcl-2-targeting antisense oligonucleotide)), IPI-194, IPI-565, N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide) (ABT-737), N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (ABT-263), GX-070 (obatoclax), ABT-199, and the like.

Bcr-Abl kinase inhibitors include DASATINIB® (BMS-354825), GLEEVEC® (imatinib) and the like.

CDK inhibitors include AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202, R-roscovitine), ZK-304709 and the like.

COX-2 inhibitors include ABT-963, ARCOXIA® (etoricoxib), BEXTRA® (valdecoxib), BMS347070, CELEBREX® (celecoxib), COX-189 (lumiracoxib), CT-3, DERAMAXX® (deracoxib), JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl-1H-pyrrole), MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX® (rofecoxib) and the like.

EGFR inhibitors include EGFR antibodies, ABX-EGF, anti-EGFR immunoliposomes, EGF-vaccine, EMD-7200, ERBITUX® (cetuximab), HR3, IgA antibodies, IRESSA® (gefitinib), TARCEVA® (erlotinib or OSI-774), TP-38, EGFR fusion protein, TYKERB® (lapatinib) and the like.

ErbB2 receptor inhibitors include CP-724-714, CI-1033 (canertinib), HERCEPTIN® (trastuzumab), TYKERB® (lapatinib), OMNITARG® (2C4, petuzumab), TAK-165, GW-572016 (ionafarnib), GW-282974, EKB-569, PI-166, dHER2 (HER2 vaccine), APC-8024 (HER-2 vaccine), anti-HER/2neu bispecific antibody, B7.her2IgG3, AS HER2 trifunctional bispecfic antibodies, mAB AR-209, mAB 2B-1 and the like.

Histone deacetylase inhibitors include depsipeptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, valproic acid and the like.

HSP-90 inhibitors include 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, MYCOGRAB® (human recombinant antibody to HSP-90), NCS-683664, PU24FCl, PU-3, radicicol, SNX-2112, STA-9090 VER49009 and the like.

Inhibitors of inhibitors of apoptosis proteins include HGS1029, GDC-0145, GDC-0152, LCL-161, LBW-242 and the like.

Antibody drug conjugates include anti-CD22-MC-MMAF, anti-CD22-MC-MMAE, anti-CD22-MCC-DM1, CR-011-vcMMAE, PSMA-ADC, MEDI-547, SGN-19Am SGN-35, SGN-75 and the like

Activators of death receptor pathway include TRAIL, antibodies or other agents that target TRAIL or death receptors (e.g., DR4 and DR5) such as Apomab, conatumumab, ETR2-ST01, GDC0145, (lexatumumab), HGS-1029, LBY-135, PRO-1762 and trastuzumab.

Kinesin inhibitors include Eg5 inhibitors such as AZD4877, ARRY-520; CENPE inhibitors such as GSK923295A and the like.

JAK-2 inhibitors include CEP-701 (lesaurtinib), XL019 and INCB018424 and the like.

MEK inhibitors include ARRY-142886, ARRY-438162 PD-325901, PD-98059 and the like.

mTOR inhibitors include AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30, Torin 1 and the like.

Non-steroidal anti-inflammatory drugs include AMIGESIC® (salsalate), DOLOBID® (diflunisal), MOTRIN® (ibuprofen), ORUDIS® (ketoprofen), RELAFEN® (nabumetone), FELDENE® (piroxicam), ibuprofen cream, ALEVE® (naproxen) and NAPROSYN® (naproxen), VOLTAREN® (diclofenac), INDOCIN® (indomethacin), CLINORIL® (sulindac), TOLECTIN® (tolmetin), LODINE® (etodolac), TORADOL® (ketorolac), DAYPRO® (oxaprozin) and the like.

PDGFR inhibitors include C-451, CP-673, CP-868596 and the like.

Platinum chemotherapeutics include cisplatin, ELOXATIN® (oxaliplatin) eptaplatin, lobaplatin, nedaplatin, PARAPLATIN® (carboplatin), satraplatin, picoplatin and the like.

Polo-like kinase inhibitors include BI-2536 and the like.

Phosphoinositide-3 kinase (PI3K) inhibitors include wortmannin, LY294002, XL-147, CAL-120, ONC-21, AEZS-127, ETP-45658, PX-866, GDC-0941, BGT226, BEZ235, XL765 and the like.

Thrombospondin analogs include ABT-510, ABT-567, ABT-898, TSP-1 and the like.

VEGFR inhibitors include AVASTIN® (bevacizumab), ABT-869, AEE-788, ANGIOZYME™ (a ribozyme that inhibits angiogenesis (Ribozyme Pharmaceuticals (Boulder, CO.) and Chiron, (Emeryville, CA)), axitinib (AG-13736), AZD-2171, CP-547,632, IM-862, MACUGEN (pegaptamib), NEXAVAR® (sorafenib, BAY43-9006), pazopanib (GW-786034), vatalanib (PTK-787, ZK-222584), SUTENT® (sunitinib, SU-11248), VEGF trap, ZACTIMA™ (vandetanib, ZD-6474), GA101, ofatumumab, ABT-806 (mAb-806), ErbB3 specific antibodies, BSG2 specific antibodies, DLL4 specific antibodies and C-met specific antibodies, and the like.

Antibiotics include intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, BLENOXANE® (bleomycin), daunorubicin, CAELYX® or MYOCET® (liposomal doxorubicin), elsamitrucin, epirbucin, glarbuicin, ZAVEDOS® (idarubicin), mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, VALSTAR® (valrubicin), zinostatin and the like.

Topoisomerase inhibitors include aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, CAMPTOSAR® (irinotecan hydrochloride), camptothecin, CARDIOXANE® (dexrazoxine), diflomotecan, edotecarin, ELLENCE® or PHARMORUBICIN® (epirubicin), etoposide, exatecan, 10-hydroxycamptothecin,

gimatecan, lurtotecan, mitoxantrone, orathecin, pirarbucin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan and the like.

Antibodies include AVASTIN® (bevacizumab), CD40-specific antibodies, chTNT-1/B, denosumab, ERBITUX® (cetuximab), HUMAX-CD4® (zanolimumab), IGF1R-specific antibodies, lintuzumab, PANOREX® (edrecolomab), RENCAREX® (WX G250), RITUXAN® (rituximab), ticilimumab, trastuzimab, CD20 antibodies types I and II and the like.

Hormonal therapies include ARIMIDEX® (anastrozole), AROMASIN® (exemestane), arzoxifene, CASODEX® (bicalutamide), CETROTIDE® (cetrorelix), degarelix, deslorelin, DESOPAN® (trilostane), dexamethasone, DROGENIL® (flutamide), EVISTA® (raloxifene), AFEMA™ (fadrozole), FARESTON® (toremifene), FASLODEX® (fulvestrant), FEMARA® (letrozole), formestane, glucocorticoids, HECTOROL® (doxercalciferol), RENAGEL® (sevelamer carbonate), lasofoxifene, leuprolide acetate, MEGACE® (megesterol), MIFEPREX® (mifepristone), NILANDRON™ (nilutamide), NOLVADEX® (tamoxifen citrate), PLENAXIS™ (abarelix), prednisone, PROPECIA® (finasteride), rilostane, SUPREFACT® (buserelin), TRELSTAR® (luteinizing hormone releasing hormone (LHRH)), VANTAS® (Histrelin implant), VETORYL® (trilostane or modrastane), ZOLADEX® (fosrelin, goserelin) and the like.

Deltoids and retinoids include seocalcitol (EB1089, CB1093), lexacalcitrol (KH1060), fenretinide, PANRETIN® (aliretinoin), ATRAGEN® (liposomal tretinoin), TARGRETIN® (bexarotene), LGD-1550 and the like.

PARP inhibitors include ABT-888 (veliparib), olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 and the like.

Plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine, vinorelbine and the like.

Proteasome inhibitors include VELCADE® (bortezomib), MG132, NPI-0052, PR-171 and the like.

Examples of immunologicals include interferons and other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, ACTIMMUNE® (interferon gamma-1b) or interferon gamma-n1, combinations thereof and the like. Other agents include ALFAFERONE®,(IFN-α), BAM-002 (oxidized glutathione), BEROMUN® (tasonermin),

BEXXAR® (tositumomab), CAMPATH® (alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), decarbazine, denileukin, epratuzumab, GRANOCYTE® (lenograstim), lentinan, leukocyte alpha interferon, imiquimod, MDX-010 (anti-CTLA-4), melanoma vaccine, mitumomab, molgramostim, MYLOTARG™ (gemtuzumab ozogamicin), NEUPOGEN® (filgrastim), OncoVAC-CL, OVAREX® (oregovomab), pemtumomab (Y-muHMFG1), PROVENGE® (sipuleucel-T), sargaramostim, sizofilan, teceleukin, THERACYS® (Bacillus Calmette-Guerin), ubenimex, VIRULIZIN® (immunotherapeutic, Lorus Pharmaceuticals), Z-100 (Specific Substance of Maruyama (SSM)), WF-10 (Tetrachlorodecaoxide (TCDO)), PROLEUKIN® (aldesleukin), ZADAXIN® (thymalfasin), ZENAPAX® (daclizumab), ZEVALIN® (90Y-Ibritumomab tiuxetan) and the like.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth or differentiation of tissue cells to direct them to have anti-tumor activity and include krestin, lentinan, sizofiran, picibanil PF-3512676 (CpG-8954), ubenimex and the like.

Pyrimidine analogs include cytarabine (ara C or Arabinoside C), cytosine arabinoside, doxifluridine, FLUDARA® (fludarabine), 5-FU (5-fluorouracil), floxuridine, GEMZAR® (gemcitabine), TOMUDEX® (ratitrexed), TROXATYL™ (triacetyluridine troxacitabine) and the like.

Purine analogs include LANVIS® (thioguanine) and PURI-NETHOL® (mercaptopurine).

Antimitotic agents include batabulin, epothilone D (KOS-862), N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone (BMS 247550), paclitaxel, TAXOTERE® (docetaxel), PNU100940 (109881), patupilone, XRP-9881 (larotaxel), vinflunine, ZK-EPO (synthetic epothilone) and the like.

Ubiquitin ligase inhibitors include MDM2 inhibitors, such as nutlins, NEDD8 inhibitors such as MLN4924 and the like.

Compounds of this invention can also be used as radiosensitizers that enhance the efficacy of radiotherapy. Examples of radiotherapy include external beam radiotherapy, teletherapy, brachytherapy and sealed, unsealed source radiotherapy and the like.

Additionally, compounds having Formula (I) may be combined with other chemotherapeutic agents such as ABRAXANE™ (ABI-007), ABT-100 (farnesyl transferase inhibitor), ADVEXIN® (Ad5CMV-p53 vaccine), ALTOCOR® or MEVACOR® (lovastatin), AMPLIGEN® (poly I:poly C12U, a synthetic RNA),

APTOSYN® (exisulind), AREDIA® (pamidronic acid), arglabin, L-asparaginase, atamestane (1-methyl-3,17-dione-androsta-1,4-diene), AVAGE® (tazarotene), AVE-8062 (combreastatin derivative) BEC2 (mitumomab), cachectin or cachexin (tumor necrosis factor), canvaxin (vaccine), CEAVAC® (cancer vaccine), CELEUK® (celmoleukin), CEPLENE® (histamine dihydrochloride), CERVARIX® (human papillomavirus vaccine), CHOP® (C: CYTOXAN® (cyclophosphamide); H: ADRIAMYCIN® (hydroxydoxorubicin); O: Vincristine (ONCOVIN®); P: prednisone), CYPAT™ (cyproterone acetate), combrestatin A4P, DAB(389)EGF (catalytic and translocation domains of diphtheria toxin fused via a His-Ala linker to human epidermal growth factor) or TransMID-107R™ (diphtheria toxins), dacarbazine, dactinomycin, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), eniluracil, EVIZON™ (squalamine lactate), DIMERICINE® (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EPO906 (epithilone B), GARDASIL® (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine), GASTRIMMUNE®, GENASENSE®, GMK (ganglioside conjugate vaccine), GVAX® (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin besudotox), IL-13-pseudomonas exotoxin, interferon-α, interferon-γ, JUNOVAN™ or MEPACT™ (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine), NEOVASTAT®(AE-941), NEUTREXIN® (trimetrexate glucuronate), NIPENT® (pentostatin), ONCONASE® (a ribonuclease enzyme), ONCOPHAGE® (melanoma vaccine treatment), ONCOVAX® (IL-2 Vaccine), ORATHECIN™ (rubitecan), OSIDEM® (antibody-based cell drug), OVAREX® MAb (murine monoclonal antibody), paclitaxel, PANDIMEX™ (aglycone saponins from ginseng comprising 20(S)protopanaxadiol (aPPD) and 20(S)protopanaxatriol (aPPT)), panitumumab, PANVAC®-VF (investigational cancer vaccine), pegaspargase, PEG Interferon A, phenoxodiol, procarbazine, rebimastat, REMOVAB® (catumaxomab), REVLIMID® (lenalidomide), RSR13 (efaproxiral), SOMATULINE® LA (lanreotide), SORIATANE® (acitretin), staurosporine (Streptomyces staurospores), talabostat (PT100), TARGRETIN® (bexarotene), TAXOPREXIN® (DHA-paclitaxel), TELCYTA® (canfosfamide, TLK286), temilifene, TEMODAR® (temozolomide), tesmilifene, thalidomide, THERATOPE® (STn-KLH), thymitaq (2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride), TNFERADE™ (adenovector: DNA carrier containing the gene for tumor necrosis factor-α), TRACLEER® or ZAVESCA® (bosentan), tretinoin (Retin-A), tetrandrine, TRISENOX® (arsenic trioxide),

VIRULIZIN®, ukrain (derivative of alkaloids from the greater celandine plant), vitaxin (anti-alphavbeta3 antibody), XCYTRIN® (motexafin gadolinium), XINLAY™ (atrasentan), XYOTAX™ (paclitaxel poliglumex), YONDELIS® (trabectedin), ZD-6126, ZINECARD® (dexrazoxane), ZOMETA® (zolendronic acid), zorubicin and the like.

The compounds of the invention can also be co-administered with a therapeutically effective amount of one or more agents to treat an inflammatory disease or condition, or autoimmune disease, where examples of the agents include, such as methotrexate, tofacitinib, 6-mercaptopurine, azathioprine sulphasalazine, mesalazine, olsalazine chloroquinine/ hydroxychloroquine, pencillamine, aurothiomalate (intramuscular and oral), azathioprine, cochicine, corticosteroids (oral, inhaled and local injection), beta-2 adrenoreceptor agonists (salbutamol, terbutaline, salmeteral), xanthines (theophylline, aminophylline), cromoglycate, nedocromil, ketotifen, ipratropium and oxitropium, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signalling by proinflammatory cytokines such as TNF□ or IL-1 (e.g., NIK, IKK, p38 or MAP kinase inhibitors), IL-1□ converting enzyme inhibitors, T-cell signalling inhibitors such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors and derivatives thereof (e.g. soluble p55 or p75 TNF receptors and the derivatives p75TNFRIgG (etanercept) and p55TNFRIgG (Lenercept), sIL-1RI, sIL-1RII, sIL-6R), antiinflammatory cytokines (e.g. IL-4, IL-10, IL-11, IL-13 and TGF□), celecoxib, folic acid, hydroxychloroquine sulfate, rofecoxib, etanercept, infliximab, adalimumab, certolizumab, tocilizumab, abatacept, naproxen, valdecoxib, sulfasalazine, methylprednisolone, meloxicam, methylprednisolone acetate, gold sodium thiomalate, aspirin, triamcinolone acetonide, propoxyphene napsylate/apap, folate, nabumetone, diclofenac, piroxicam, etodolac, diclofenac sodium, oxaprozin, oxycodone HCl, hydrocodone bitartrate/apap, diclofenac sodium/misoprostol, fentanyl, anakinra, tramadol HCl, salsalate, sulindac, cyanocobalamin/fa/pyridoxine, acetaminophen, alendronate sodium, prednisolone, cortisone, betamethasone, morphine sulfate, lidocaine hydrochloride, indomethacin, glucosamine sulf/chondroitin, amitriptyline HCl, sulfadiazine, oxycodone HCl/acetaminophen, olopatadine HCl misoprostol, naproxen sodium, omeprazole, cyclophosphamide, rituximab, IL-1 TRAP, MRA, CTLA4-IG, IL-18 BP, anti-IL-12, Anti-IL15, BIRB-796, SCIO-469, VX-702, AMG-548, VX-740,

Roflumilast, IC-485, CDC-801, S1P1 agonists (such as FTY720), PKC family inhibitors (such as Ruboxistaurin or AEB-071) and Mesopram. In certain embodiments, combinations include methotrexate or leflunomide and in moderate or severe rheumatoid arthritis cases, cyclosporine and anti-TNF antibodies as noted above.

Non-limiting examples of therapeutic agents for inflammatory bowel disease with which a compound of Formula (I) of the invention may be co-administered include the following: budenoside; epidermal growth factor; corticosteroids; cyclosporin, sulfasalazine; aminosalicylates; 6-mercaptopurine; azathioprine; metronidazole; lipoxygenase inhibitors; mesalamine; olsalazine; balsalazide; antioxidants; thromboxane inhibitors; IL-1 receptor antagonists; anti-IL-1□ monoclonal antibodies; anti-IL-6 monoclonal antibodies; growth factors; elastase inhibitors; pyridinyl-imidazole compounds; antibodies to or antagonists of other human cytokines or growth factors, for example, TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-15, IL-16, IL-23, EMAP-II, GM-CSF, FGF, and PDGF; cell surface molecules such as CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands; methotrexate; cyclosporine; FK506; rapamycin; mycophenolate mofetil; leflunomide; NSAIDs, for example, ibuprofen; corticosteroids such as prednisolone; phosphodiesterase inhibitors; adenosine agonists; antithrombotic agents; complement inhibitors; adrenergic agents; agents which interfere with signalling by proinflammatory cytokines such as TNF□ or IL-1 (e.g. NIK, IKK, or MAP kinase inhibitors); IL-1□ converting enzyme inhibitors; TNF□ converting enzyme inhibitors; T-cell signalling inhibitors such as kinase inhibitors; metalloproteinase inhibitors; sulfasalazine; azathioprine; 6-mercaptopurines; angiotensin converting enzyme inhibitors; soluble cytokine receptors and derivatives thereof (e.g. soluble p55 or p75 TNF receptors, sIL-1RI, sIL-1RII, sIL-6R) and antiinflammatory cytokines (e.g. IL-4, IL-10, IL-11, IL-13 and TGF□). Preferred examples of therapeutic agents for Crohn's disease with which a compound of Formula (I) can be combined include the following: TNF antagonists, for example, anti-TNF antibodies, D2E7 (adalimumab), CA2 (infliximab), CDP 571, TNFR-Ig constructs, (p75TNFRIgG (etanercept) and p55TNFRIgG (LENERCEPT^{TM}) inhibitors and PDE4 inhibitors. A compound of Formula (I) can be combined with corticosteroids, for example, budenoside and dexamethasone; sulfasalazine, 5-aminosalicylic acid; olsalazine; and agents which interfere with synthesis or action of proinflammatory cytokines such as IL-1, for example, IL-1□ converting enzyme inhibitors and IL-1ra; T cell signaling inhibitors, for example, tyrosine kinase

inhibitors; 6-mercaptopurine; IL-11; mesalamine; prednisone; azathioprine; mercaptopurine; infliximab; methylprednisolone sodium succinate; diphenoxylate/atrop sulfate; loperamide hydrochloride; methotrexate; omeprazole; folate; ciprofloxacin/dextrose-water; hydrocodone bitartrate/apap; tetracycline hydrochloride; fluocinonide; metronidazole; thimerosal/boric acid; cholestyramine/sucrose; ciprofloxacin hydrochloride; hyoscyamine sulfate; meperidine hydrochloride; midazolam hydrochloride; oxycodone HCl/acetaminophen; promethazine hydrochloride; sodium phosphate; sulfamethoxazole/trimethoprim; celecoxib; polycarbophil; propoxyphene napsylate; hydrocortisone; multivitamins; balsalazide disodium; codeine phosphate/apap; colesevelam HCl; cyanocobalamin; folic acid; levofloxacin; methylprednisolone; natalizumab and interferon-gamma.

Non-limiting examples of therapeutic agents for multiple sclerosis with which a compound of Formula (I) may be co-administered include the following: corticosteroids; prednisolone; methylprednisolone; azathioprine; cyclophosphamide; cyclosporine; methotrexate; 4-aminopyridine; tizanidine; interferon-□1a (AVONEX®; Biogen); interferon-□1b (BETASERON®; Chiron/Berlex); interferon □-n3) (Interferon Sciences/Fujimoto), interferon-□ (Alfa Wassermann/J&J), interferon □1A-IF (Serono/Inhale Therapeutics), Peginterferon □ 2b (Enzon/Schering-Plough), Copolymer 1 (Cop-1; COPAXONE®; Teva Pharmaceutical Industries, Inc.); hyperbaric oxygen; intravenous immunoglobulin; cladribine; antibodies to or antagonists of other human cytokines or growth factors and their receptors, for example, TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-23, IL-15, IL-16, EMAP-II, GM-CSF, FGF, and PDGF. A compound of Formula (I) can be combined with antibodies to cell surface molecules such as CD2, CD3, CD4, CD8, CD19, CD20, CD25, CD28, CD30, CD40, CD45, CD69, CD80, CD86, CD90 or their ligands. A compound of Formula (I) may also be combined with agents such as methotrexate, cyclosporine, FK506, rapamycin, mycophenolate mofetil, leflunomide, an S1P1 agonist, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signalling by proinflammatory cytokines such as TNF□ or IL-1 (e.g., NIK, IKK, p38 or MAP kinase inhibitors), IL-1□ converting enzyme inhibitors, TACE inhibitors, T-cell signaling inhibitors such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors and derivatives thereof (e.g. soluble p55 or p75 TNF receptors, sIL-

1RI, sIL-1RII, sIL-6R) and antiinflammatory cytokines (e.g. IL-4, IL-10, IL-13 and TGF□).

A compound of Formula (I) may also be co-administered with agents, such as alemtuzumab, dronabinol, daclizumab, mitoxantrone, xaliproden hydrochloride, fampridine, glatiramer acetate, natalizumab, sinnabidol, □-immunokine NNSO3, ABR-215062, AnergiX.MS, chemokine receptor antagonists, BBR-2778, calagualine, CPI-1189, LEM (liposome encapsulated mitoxantrone), THC.CBD (cannabinoid agonist), MBP-8298, mesopram (PDE4 inhibitor), MNA-715, anti-IL-6 receptor antibody, neurovax, pirfenidone allotrap 1258 (RDP-1258), sTNF-R1, talampanel, teriflunomide, TGF-beta2, tiplimotide, VLA-4 antagonists (for example, TR-14035, VLA4 Ultrahaler, Antegran-ELAN/Biogen), interferon gamma antagonists and IL-4 agonists.

Non-limiting examples of therapeutic agents for ankylosing spondylitis with which a compound of Formula (I) can be co-administered include the following: ibuprofen, diclofenac, misoprostol, naproxen, meloxicam, indomethacin, diclofenac, celecoxib, rofecoxib, sulfasalazine, methotrexate, azathioprine, minocyclin, prednisone, and anti-TNF antibodies, D2E7 (HUMIRA®), CA2 (infliximab), CDP 571, TNFR-Ig constructs, (p75TNFRIgG (ENBREL®) and p55TNFRIgG (LENERCEPT®).

Non-limiting examples of therapeutic agents for asthma with which a compound of Formula (I) may be co-administered include the following: albuterol, salmeterol/fluticasone, montelukast sodium, fluticasone propionate, budesonide, prednisone, salmeterol xinafoate, levalbuterol HCl, albuterol sulfate/ipratropium, prednisolone sodium phosphate, triamcinolone acetonide, beclomethasone dipropionate, ipratropium bromide, azithromycin, pirbuterol acetate, prednisolone, theophylline anhydrous, methylprednisolone sodium succinate, clarithromycin, zafirlukast, formoterol fumarate, influenza virus vaccine, amoxicillin trihydrate, flunisolide, allergy injection, cromolyn sodium, fexofenadine hydrochloride, flunisolide/menthol, amoxicillin/clavulanate, levofloxacin, inhaler assist device, guaifenesin, dexamethasone sodium phosphate, moxifloxacin HCl, doxycycline hyclate, guaifenesin/d-methorphan, p-ephedrine/cod/chlorphenir, gatifloxacin, cetirizine hydrochloride, mometasone furoate, salmeterol xinafoate, benzonatate, cephalexin, pe/hydrocodone/chlorphenir, cetirizine HCl/pseudoephed, phenylephrine/cod/promethazine, codeine/promethazine, cefprozil, dexamethasone, guaifenesin/pseudoephedrine, chlorpheniramine/hydrocodone, nedocromil sodium, terbutaline sulfate, epinephrine, methylprednisolone, anti-IL-13 antibody, and metaproterenol sulfate.

$-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})C(O)O(R^{2d})$, $-N(R^{2e})C(O)NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, $-(C_1\text{-}C_6$ alkylenyl)-G^{2a}, $-(C_1\text{-}C_6$ alkylenyl)-OR^{2a}, $-(C_1\text{-}C_6$ alkylenyl)-$OC(O)R^{2d}$, $-(C_1\text{-}C_6$ alkylenyl)-$OC(O)NR^{2b}R^{2c}$, $-(C_1\text{-}C_6$ alkylenyl)-$S(O)_2R^{2d}$, $-(C_1\text{-}C_6$ alkylenyl)-$S(O)_2NR^{2b}R^{2c}$, $-(C_1\text{-}C_6$ alkylenyl)-$C(O)R^{2d}$, $-(C_1\text{-}C_6$ alkylenyl)-$C(O)OR^{2a}$, $-(C_1\text{-}C_6$ alkylenyl)-$C(O)NR^{2b}R^{2c}$, $-(C_1\text{-}C_6$ alkylenyl)-$NR^{2b}R^{2c}$, $-(C_1\text{-}C_6$ alkylenyl)-$N(R^{2e})C(O)R^{2d}$, $-(C_1\text{-}C_6$ alkylenyl)-$N(R^{2e})S(O)_2R^{2d}$, $-(C_1\text{-}C_6$ alkylenyl)-$N(R^{2e})C(O)O(R^{2a})$, $-(C_1\text{-}C_6$ alkylenyl)-$N(R^{2e})C(O)NR^{2b}R^{2c}$, $-(C_1\text{-}C_6$ alkylenyl)-$N(R^{2e})S(O)_2NR^{2b}R^{2c}$, and $-(C_1\text{-}C_6$ alkylenyl)-CN;

R^{2a}, R^{2b}, R^{2c}, and R^{2e}, at each occurrence, are each independently hydrogen, $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, $C_1\text{-}C_6$ haloalkyl, G^{2b}, or $C_1\text{-}C_6$ alkyl wherein the $C_1\text{-}C_6$ alkyl is optionally substituted with one substituent selected from the group consisting of $-OR^{z1}$, $NR^{z1}R^{z2}$, $-C(O)OR^{z1}$, $-C(O)NR^{z1}R^{z2}$, $-S(O)_2R^{z1}$, $-S(O)_2NR^{z1}R^{z2}$, and G^{2b};

R^{2d}, at each occurrence, is independently $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, $C_1\text{-}C_6$ haloalkyl, G^{2b}, or $C_1\text{-}C_6$ alkyl wherein the $C_1\text{-}C_6$ alkyl is optionally substituted with one substituent selected from the group consisting of $-OR^{z1}$, $NR^{z1}R^{z2}$, $-C(O)OR^{z1}$, $-C(O)NR^{z1}R^{z2}$, $-S(O)_2R^{z1}$, $-S(O)_2NR^{z1}R^{z2}$, and G^{2b};

R^{z1} and R^{z2}, at each occurrence, are each independently hydrogen, $C_1\text{-}C_6$ alkyl, or $C_1\text{-}C_6$ haloalkyl;

G^{x1}, G^{x2}, G^a, G^b, G^{2a}, and G^{2b}, at each occurrence, are each independently aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl, and each of which is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 of R^v;

L^1 is absent, CH_2, C(O), $(CH_2)_mO$, $(CH_2)_mS(O)_n$ wherein n is 0, 1, or 2; or $(CH_2)_mN(R^z)$ wherein R^z is hydrogen, $C_1\text{-}C_3$ alkyl, $C_1\text{-}C_3$ haloalkyl, $(C_2\text{-}C_3$ alkylenyl)-OH, or unsubstituted cyclopropyl;

m is 0 or 1;

G^1 is G^{1a} or $-(C_1\text{-}C_6$ alkylenyl)-G^{1a}; wherein each G^{1a} is independently aryl, heteroaryl, heterocycle, cycloalkyl, or cycloalkenyl, and each G^{1a} is independently unsubstituted or substituted with 1, 2, 3, 4, or 5 of R^w;

R^v and R^w, at each occurrence, are each independently $C_1\text{-}C_6$ alkyl, $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, halogen, $C_1\text{-}C_6$ haloalkyl, -CN, oxo, $-OR^h$, $-OC(O)R^i$,

Non-limiting examples of therapeutic agents for COPD with which a compound of Formula (I) may be co-administered include the following: albuterol sulfate/ipratropium, ipratropium bromide, salmeterol/fluticasone, albuterol, salmeterol xinafoate, fluticasone propionate, prednisone, theophylline anhydrous, methylprednisolone sodium succinate, montelukast sodium, budesonide, formoterol fumarate, triamcinolone acetonide, levofloxacin, guaifenesin, azithromycin, beclomethasone dipropionate, levalbuterol HCl, flunisolide, ceftriaxone sodium, amoxicillin trihydrate, gatifloxacin, zafirlukast, amoxicillin/clavulanate, flunisolide/menthol, chlorpheniramine/hydrocodone, metaproterenol sulfate, methylprednisolone, mometasone furoate, p-ephedrine/cod/chlorphenir, pirbuterol acetate, p-ephedrine/loratadine, terbutaline sulfate, tiotropium bromide, (R,R)-formoterol, TgAAT, cilomilast and roflumilast.

Non-limiting examples of therapeutic agents for psoriasis with which a compound of Formula (I) may be co-administered include the following: calcipotriene, clobetasol propionate, triamcinolone acetonide, halobetasol propionate, tazarotene, methotrexate, fluocinonide, betamethasone diprop augmented, fluocinolone acetonide, acitretin, tar shampoo, betamethasone valerate, mometasone furoate, ketoconazole, pramoxine/fluocinolone, hydrocortisone valerate, flurandrenolide, urea, betamethasone, clobetasol propionate/emoll, fluticasone propionate, azithromycin, hydrocortisone, moisturizing formula, folic acid, desonide, pimecrolimus, coal tar, diflorasone diacetate, etanercept folate, lactic acid, methoxsalen, hc/bismuth subgal/znox/resor, methylprednisolone acetate, prednisone, sunscreen, halcinonide, salicylic acid, anthralin, clocortolone pivalate, coal extract, coal tar/salicylic acid, coal tar/salicylic acid/sulfur, desoximetasone, diazepam, emollient, fluocinonide/emollient, mineral oil/castor oil/na lact, mineral oil/peanut oil, petroleum/isopropyl myristate, psoralen, salicylic acid, soap/tribromsalan, thimerosal/boric acid, celecoxib, infliximab, cyclosporine, alefacept, efalizumab, tacrolimus, pimecrolimus, PUVA, UVB, sulfasalazine, ABT-874 and ustekinamab.

Non-limiting examples of therapeutic agents for psoriatic arthritis with which a compound of Formula (I) may be co-administered include the following: methotrexate, etanercept, rofecoxib, celecoxib, folic acid, sulfasalazine, naproxen, leflunomide, methylprednisolone acetate, indomethacin, hydroxychloroquine sulfate, prednisone, sulindac, betamethasone diprop augmented, infliximab, methotrexate, folate, triamcinolone acetonide, diclofenac, dimethylsulfoxide, piroxicam, diclofenac sodium, ketoprofen, meloxicam, methylprednisolone, nabumetone, tolmetin sodium, calcipotriene,

cyclosporine, diclofenac sodium/misoprostol, fluocinonide, glucosamine sulfate, gold sodium thiomalate, hydrocodone bitartrate/apap, ibuprofen, risedronate sodium, sulfadiazine, thioguanine, valdecoxib, alefacept, D2E7 (adalimumab), and efalizumab.

Preferred examples of therapeutic agents for SLE (Lupus) with which a compound of Formula (I) may be co-administered include the following: NSAIDS, for example, diclofenac, naproxen, ibuprofen, piroxicam, indomethacin; COX2 inhibitors, for example, celecoxib, rofecoxib, valdecoxib; anti-malarials, for example, hydroxychloroquine; steroids, for example, prednisone, prednisolone, budenoside, dexamethasone; cytotoxics, for example, azathioprine, cyclophosphamide, mycophenolate mofetil, methotrexate; inhibitors of PDE4 or purine synthesis inhibitor, for example Cellcept®. A compound of Formula (I) may also be combined with agents such as sulfasalazine, 5-aminosalicylic acid, olsalazine, Imuran® and agents which interfere with synthesis, production or action of proinflammatory cytokines such as IL-1, for example, caspase inhibitors like IL-1□ converting enzyme inhibitors and IL-1ra. A compound of Formula (I) may also be used with T cell signaling inhibitors, for example, tyrosine kinase inhibitors; or molecules that target T cell activation molecules, for example, CTLA-4-IgG or anti-B7 family antibodies, anti-PD-1 family antibodies. A compound of Formula (I) can be combined with IL-11 or anti-cytokine antibodies, for example, fonotolizumab (anti-IFNg antibody), or anti-receptor receptor antibodies, for example, anti-IL-6 receptor antibody and antibodies to B-cell surface molecules. A compound of Formula (I) may also be used with LJP 394 (abetimus), agents that deplete or inactivate B-cells, for example, Rituximab (anti-CD20 antibody), lymphostat-B (anti-BlyS antibody), TNF antagonists, for example, anti-TNF antibodies, D2E7 (adalimumab), CA2 (infliximab), CDP 571, TNFR-Ig constructs, (p75TNFRIgG (etanercept) and p55TNFRIgG (LENERCEPT^{TM}).

The compounds of the invention can also be co-administered with a therapeutically effective amount of one or more agents used in the prevention or treatment of AIDS, where examples of the agents include, HIV reverse transcriptase inhibitors, HIV protease inhibitors, immunomodulators, and other retroviral drugs. Examples of reverse transcriptase inhibitors include, but are not limited to, abacavir, adefovir, didanosine, dipivoxil delavirdine, efavirenz, emtricitabine, lamivudine, nevirapine, rilpivirine, stavudine, tenofovir, zalcitabine, and zidovudine. Examples of protease inhibitors include, but are not limited to, amprenavir, atazanavir, darunavir, indinavir, fosamprenavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir. Examples of other retroviral drugs include, but are not limited to, elvitegravir, enfuvirtide, maraviroc and raltegravir.

The compounds of the invention can be co-administered with a therapeutically effective amount of one or more agents to prevent or treat type II diabetes, hepatic steatosis, insulin resistance, metabolic syndrome and related disorders, where examples of the agents include, but are not limited to, insulin and insulins that have been modified to improve the duration of action in the body; agents that stimulate insulin secretion such as acetohexamide, chlorpropamide, glyburide, glimepiride, glipizide, glicazide, glycopyramide, gliquidone, rapaglinide, nataglinide, tolazamide and tolbutamide; agents that are glucagon-like peptide agonists such as exanatide, liraglutide and taspoglutide; agents that inhibit dipeptidyl-peptidase IV such as vildagliptin, sitagliptin, saxagliptin, linagliptin, allogliptin and septagliptin; agents that bind to the peroxisome proliferator-activated receptor gamma such as rosiglitazone and pioglitazone; agents that decrease insulin resistance such as metformin; agents that reduce glucose absorbance in the small intestine such as acarbose, miglitol and voglibose.

The compounds of the invention can be co-administered with a therapeutically effective amount of one or more agents to prevent or treat acute kidney disorders and chronic kidney diseases, where examples of the agents include, but are not limited to, dopamine, diuretics such as furosemide, bumetanide, thiazide and the like, mannitol, calcium gluconate, sodium bicarbonate, albuterol, paricalcitol, doxercalciferol, cinacalcet and bardoxalone methyl.

The compounds of the invention can be co-administered with a therapeutically effective amount of one or more agents to a male subject to provide for male contraception.

The following Examples may be used for illustrative purposes and should not be deemed to narrow the scope of the invention.

Examples

Example 1

6-methyl-4-(2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 1a

(E)-2-(5-bromo-2-methoxy-3-nitropyridin-4-yl)-N,N-dimethylethenamine

5-Bromo-2-methoxy-4-methyl-3-nitropyridine (15.0 g, 60.7 mmol) was dissolved in dimethylformamide (300 mL), and lithium methanolate (6.07 mL, 6.07 mmol, 1 M) was added. The reaction mixture was heated to 100 °C. To this mixture was added 1,1-dimethoxy-N,N-dimethylmethanamine (64.5 mL, 486 mmol) over 10 minutes. The

reaction mixture was stirred at 95 °C for 16 hours. The reaction mixture was cooled to room temperature and water was added carefully (300 mL, exothermic). The resulting precipitate was collected by vacuum filtration, washed with water, and dried to provide the title compound (13.9 g, 45.9 mmol, 76 % yield).

Example 1b

4-bromo-7-methoxy-1H-pyrrolo[2,3-c]pyridine

Example 1a (13.9 g, 45.8 mmol) and ethyl acetate (150 mL) were added to Ra-Ni 2800 (pre-washed with ethanol), water slurry (6.9 g, 118 mmol) in a stainless steel pressure bottle and stirred for 30 minutes at 30 psi and room temperature. The reaction mixture was filtered, and concentrated. The residue was triturated with dichloromethane, and the solid filtered to provide the title compound (5.82 g). The mother liquor was evaporated and the residue triturated again with dichloromethane and filtered to provide an additional 1.63 g of the title compound. Total yield = 7.45 g, 72% yield.

Example 1c

4-bromo-7-methoxy-1-tosyl-1H-pyrrolo[2,3-c]pyridine

A solution of Example 1b (7.42 g, 32.7 mmol) in dimethylformamide (235 mL) was stirred at room temperature. To this solution was added sodium hydride (1.18 g, 1.96 g of 60% dispersion in oil, 49.0 mmol), and the reaction mixture was stirred for 10 min. *P*-toluenesulfonyl chloride (9.35 g, 49.0 mmol) was then added portion-wise, and the mixture was stirred at room temperature under nitrogen for 16 hours. The reaction mixture was quenched carefully with water and the resulting beige solid collected by vacuum filtration on a Buchner funnel, and washed with water. The solid was collected and dried in a vacuum oven at 50 °C to provide 12.4 g (100%) of the title compound.

Example 1d

4-bromo-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

A solution of Example 1c (12.4 g, 32.6 mmol) in dioxane (140 mL) was stirred at room temperature. To this solution was added 4M HCl in dioxane (140 mL). The reaction mixture was stirred at 40 °C for 16 hours. The reaction mixture was cooled to room temperature and concentrated. The residue was triturated with diethylether, filtered, and rinsed with additional diethylether and dried to provide the title compound (11.23 g, 30.6 mmol, 94 % yield) as a beige solid.

Example 1e

4-bromo-6-methyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Sodium hydride (0.875 g, 36.5 mmol, 1.46 g of a 60% in oil dispersion) was added to a stirring solution of Example 1d (11.2 g, 30.4 mmol) in dimethylformamide (217 mL) under nitrogen. After 30 minutes, iodomethane (2.27 mL, 36.5 mmol) was added and the solution was stirred at room temperature for 3 h. Upon addition of water (250 mL) a precipitate formed. The precipitate was collected by vacuum filtration, rinsed with water (50 mL) and dried in a vacuum oven at 55 °C overnight to provide 11.2 g of the title compound (96%).

Example 1f

6-methyl-4-(2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

A mixture of Example 1e (152 mg, 0.40 mmol), 2-phenoxyphenylboronic acid (0.111 g, 0.520 mmol, 1.3 equivalents), $Pd(PPh_3)_4$ (0.023 g, 5 mol%) and cesium fluoride (0.182 g, 1.2 mmol) in DME (3 mL) and methanol (1.5 mL) was heated under microwave condition (120 °C, 30 minutes). To this mixture was added potassium carbonate (0.055 g, 0.40 mmol) and water (1 mL) and the reaction mixture was reheated in the microwave oven at 120 °C for another 2 hours. The organic layer was separated and purified by flash chromatography (silica gel, ethyl acetate). The resulting material was triturated with acetone and filtered to provide 0.075 g of the title compound (59%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.50 (s, 3 H), 6.21-6.23 (m, 1 H), 6.88 (d, J=7.62 Hz, 2 H), 6.99-7.04 (m, 2 H), 7.24-7.30 (m, 5 H), 7.36-7.40 (m, 1 H), 7.50 (dd, J=7.48, 1.68 Hz, 1H), 11.98 (s, 1 H). MS (ESI+) m/z 317 $(M+H)^+$.

Example 2

6-methyl-4-(5-nitro-2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 2a

4-(2-fluoro-5-nitrophenyl)-6-methyl-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Method A:

Example 1e (0.687 g, 1.802 mmol), 2-fluoro-5-nitrophenylboronic acid (0.500 g, 2.70 mmol), $Pd(PPh_3)_4$ (0.104 g, 0.090 mmol) and sodium carbonate (2.70 mL, 5.41 mmol) were combined in DME (7 mL) and water (7 mL) in a 20 mL microwave tube, sealed, sparged with nitrogen and heated under microwave at 120 °C for 30 minutes. The mixture was partitioned between EtAOc and water. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography (silica gel, 0-100% ethyl acetate in hexanes) to provide 0.41 g (52%) of the title compound.

Method B:

Example 1e (6.00 g, 15.7 mmol), 2-fluoro-5-nitrophenylboronic acid (5.82 g, 31.5 mmol), $Pd(PPh_3)_4$ (0.909 g, 0.787 mmol) and sodium carbonate (3.34 g, 31.5 mmol) were combined in toluene (60 mL), ethanol (15 mL) and water (15 mL) and the mixture was degassed and left under nitrogen. The reaction mixture was heated at 90 °C overnight, and then cooled to room temperature. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography (silica gel, 20-50% ethyl acetate in hexanes) to provide 6.95 g (61%) of the title compound.

Example 2b

6-methyl-4-(5-nitro-2-phenoxyphenyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Phenol (0.094 g, 0.997 mmol), Example 2a (0.4 g, 0.906 mmol) and cesium carbonate (0.325 g, 0.997 mmol) were combined in DMSO (4.53 mL) and heated at 100 °C for 2 hours. The reaction mixture was partitioned between ethyl acetate and water and pH was adjusted to pH 7. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography (silica gel, 0-4 % methanol in dichloromethane) afforded 0.28 g (84%) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.57 (s, 3 H) 6.28 - 6.34 (m, 1 H) 6.98 (d, J=9.12 Hz, 1 H) 7.16 (d, J=7.54 Hz, 2 H) 7.21 - 7.32 (m, 2 H) 7.40 - 7.49 (m, 3 H) 8.22 (dd, J=9.12, 2.78 Hz, 1 H) 8.32 (d, J=2.78 Hz, 1 H) 12.07 - 12.11 (m, 1 H). MS (ESI+) m/z 362 $[M+H]^+$

Example 3

4-(5-amino-2-phenoxyphenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one

Example 2b (0.25 g, 0.692 mmol), iron powder (0.193 g, 3.46 mmol), and ammonium chloride (0.056 g, 1.038 mmol) were combined in tetrahydrofuran (6 mL), ethanol (6 mL) and water (2 mL). The mixture was heated at 95 °C with vigorous stirring for 1.5 hours. The reaction mixture was cooled to room temperature and filtered through a plug of Celite to remove solids. The plug was rinsed repeatedly with methanol and tetrahydrofuran. The filtrate was concentrated and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1-4 % methanol in dichloromethane) to afford 0.21 g (82 %) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.43 (s, 3 H) 5.07 (s, 2 H) 6.22 - 6.25 (m, 1 H) 6.59 (dd, J=8.48,

2.71 Hz, 1 H) 6.68 (d, J=7.80 Hz, 2 H) 6.74 (d, J=2.71 Hz, 1 H) 6.80 - 6.88 (m, 2 H) 7.11 - 7.19 (m, 3 H) 7.24 (t, J=2.71 Hz, 1 H) 11.91 (s, 1 H). MS (ESI+) m/z 362 $[M+H]^+$.

Example 4

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]methanesulfonamide

Method A:

To a solution of Example 3 (0.125 g, 0.377 mmol) and triethylamine (0.131 mL, 0.943 mmol) in dichloromethane (3.0 mL) was added dropwise methanesulfonyl chloride (0.064 mL, 0.830 mmol). The reaction mixture was stirred for 2 hours at ambient temperature and then concentrated. The residue was dissolved in a mixture of dioxane (5 mL) and 1M sodium hydroxide (2 mL) and heated for 1 hour at 90 °C. The reaction mixture was cooled and diluted with ethyl acetate, brought to pH 7 with 1 M HCl and partitioned. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 0-4 % methanol in dichloromethane) to afford 0.20 g (77 %) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.02 (s, 3 H) 3.48 (s, 3 H) 6.23 - 6.30 (m, 1 H) 6.85 (d, J=7.46 Hz, 2 H) 6.99 (t, J=7.29 Hz, 1 H) 7.04 (d, J=8.82 Hz, 1 H) 7.20 - 7.29 (m, 5 H) 7.39 (d, J=2.71 Hz, 1 H) 9.72 (s, 1 H) 12.01 (s, 1 H). MS (ESI+) m/z 410 $[M+H]^+$.

Method B:

The product of Example 7d (1.127 g, 2 mmol), potassium hydroxide (1.82 g, 52.5 mmol) and cetyltrimethylammonium bromide (0.036 g, 0.100 mmol) were combined in tetrahydrofuran (15.00 mL) and water (5.00 mL) and the mixture heated at 100 °C for 14 hours. The reaction mixture was partitioned between equal volumes of EtOAc and water and the pH was adjusted to pH 7 by careful addition of concentrated HCl. The organic layer was separated, washed three times with saturated brine, dried (Na_2SO_4) and concentrated. Purification by trituration in dichloromethane afforded the title compound (0.76 g, 93%).

Example 5

2,2,2-trifluoro-N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]ethanesulfonamide

To a solution of Example 3 (0.05 g, 0.151 mmol) and triethylamine (0.053 mL, 0.377 mmol) in dichloromethane (1.0 mL) was added dropwise 2,2,2-trifluoroethanesulfonyl chloride (0.036 g, 0.196 mmol). The reaction mixture was stirred for 1 hour at room temperature and then purified by flash chromatography (silica gel, 0-

5% methanol in dichloromethane) to afford 0.050 g (68 %) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.49 (s, 3 H) 4.55 (q, J=9.91 Hz, 2 H) 6.28 (t, J=2.38 Hz, 1 H) 6.86 (d, J=7.54 Hz, 2 H) 6.95 - 7.07 (m, 2 H) 7.20 - 7.31 (m, 5 H) 7.40 (d, J=2.78 Hz, 1 H) 10.43 (s, 1 H) 12.02 (s, 1 H). MS (APCI+) m/z 478 $[M+H]^+$.

Example 6

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]acetamide

Example 6a

6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one

Example 1e (6.55 g, 17.2 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (8.73 g, 34.4 mmol), potassium acetate (3.71 g, 37.8 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.393 g, 0.430 mmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-PHOS, 0.819 g, 1.72 mmol) were combined and sparged with argon for 1 hour with stirring. Dioxane (86 mL) was sparged with nitrogen for 1 hour, transferred via canula under nitrogen to the solid components, and the mixture was heated under argon at 80 °C for 5 hours. The reaction mixture was cooled to room temperature, partitioned between ethyl acetate and water, and filtered through Celite. The ethyl acetate layer was washed twice with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by chromatography (silica gel, 25-80% ethyl acetate in hexane). The resulting material from chromatography was triturated with a minimal amount of hexanes (30 mL) and the particulate solid was collected by filtration, rinsed with a minimal amount of hexanes and dried to constant mass to afford the title compound (5.4 g, 73%).

Example 6b

N-(3-bromo-4-phenoxyphenyl)acetamide

Example 7b (0.2 g, 0.757 mmol), and acetic anhydride (1 mL, 10.60 mmol) were combined in a 5 mL microwave tube, sealed and heated under microwave at 100 °C for 30 minutes. The mixture was concentrated and the residue was purified by chromatography (silica gel, 0-50% ethyl acetate in hexanes) to afford the title compound (0.22 g, 95%).

Example 6c

N-(3-(6-methyl-7-oxo-1-tosyl-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl)acetamide

Example 6a (0.07 g, 0.163 mmol), Example 6b (0.075 g, 0.245 mmol), tetrakis(triphenylphosphine)palladium(0) (9.44 mg, 8.17 μmol) and sodium carbonate (2.0 M, 0.245 mL, 0.490 mmol) were combined in DME (0.817 mL) and water (0.817 mL) in a 5 mL microwave tube, sealed, sparged with nitrogen and heated under microwave at 120 °C for 30 minutes. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography (silica gel, 0-5% methanol in dichloromethane) afforded the title compound (0.048 g, 56%).

Example 6d

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-phenoxyphenyl]acetamide

Example 6c (0.048 g, 0.091 mmol) and potassium carbonate (0.044 g, 0.318 mmol) were combined in methanol (2 mL) and water (0.200 mL) in a 2 mL microwave tube, sealed, and heated under microwave at 110 °C for 30 minutes. The reaction mixture was concentrated and the residue partitioned between ethyl acetate and water, adjusting the pH to 6 with 1M HCl. The organic layer was separated and concentrated. Purification by flash chromatography (silica gel, 0-4 % methanol in dichloromethane) afforded 0.018 g (53%) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.05 (s, 3 H) 3.48 (s, 3 H) 6.25 - 6.30 (m, 1 H) 6.80 (d, J=7.46 Hz, 2 H) 6.96 (t, J=7.29 Hz, 1 H) 7.01 (d, J=8.82 Hz, 1 H) 7.18 - 7.31 (m, 4 H) 7.56 (dd, J=8.65, 2.54 Hz, 1 H) 7.79 (d, J=2.71 Hz, 1 H) 10.04 (s, 1 H) 11.97 (s, 1 H). MS (ESI+) m/z 374 $[M+H]^+$.

Example 7

N-(3-{6-methyl-1-[(4-methylphenyl)sulfonyl]-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl}-4-phenoxyphenyl)methanesulfonamide

Example 7a

2-bromo-4-nitro-1-phenoxybenzene

2-Bromo-1-fluoro-4-nitrobenzene (2.5 g, 11.4 mmol), phenol (1.28 g, 13.6 mmol), and cesium carbonate (4.44 g, 13.6 mmol) were combined in dimethylsulfoxide (140 mL) and heated to 110 °C for 1 hour. The reaction mixture was partitioned between ethyl acetate and brine. The combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated to afford the title compound.

Example 7b

3-bromo-4-phenoxyaniline

Example 7a (3.43 g, 11.7 mmol), iron powder (3.26 g, 58.4 mmol), and ammonium chloride (1.25 g, 23.4 mmol) were combined in ethanol (50 mL),tetrahydrofuran (50 mL), and water (16.7 mL), and heated at 100 °C for 2 hour. The reaction mixture was cooled to just below reflux, vacuum filtered through diatomaceous earth, the filter cake washed with warm methanol (3x35 mL), and the filtrate concentrated under reduced pressure. The residue was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate (3 x 125 mL). The combined organics were washed with brine, dried ($MgSO_4$), gravity filtered then concentrated to afford the title compound.

Example 7c

N-(3-bromo-4-phenoxyphenyl)methanesulfonamide

Example 7b (2.86 g, 10.8 mmol) and triethylamine (6.03 mL, 43.3 mmol) were stirred in dichloromethane (48.1 mL) at ambient temperature. Methanesulfonyl chloride (2.53 mL, 32.4 mmol) was added dropwise and the solution stirred at ambient temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, dioxane (24 mL) and sodium hydroxide (10 % w/v, 12 mL, 0.427 mmol) were added, and the solution was heated to 70 °C for 1 h. The solution was neutralized to a pH of 7 with saturated aqueous NH_4Cl (200 mL). The aqueous phase was extracted with ethyl acetate (3x125 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered, then concentrated. The residue was purified by flash chromatography (silica gel, 0-25% ethyl acetate/hexane gradient,) to afford the title compound.

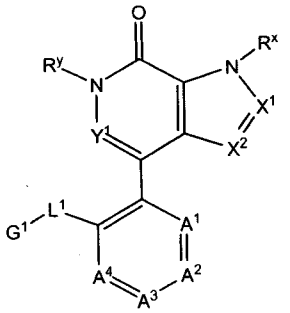
Example 7d

N-(3-{6-methyl-1-[(4-methylphenyl)sulfonyl]-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl}-4-phenoxyphenyl)methanesulfonamide

Example 6a (0.670 g, 1.564 mmol), Example 7c (0.562 g, 1.643 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.036 g, 0.039 mmol), 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamante (0.023 g, 0.078 mmol) and potassium phosphate tribasic (1.03 g, 4.85 mmol) were combined and sparged with argon for 30 minutes. A solution of 4:1 dioxane/water (10 mL total volume) was sparged with nitrogen for 30 minutes and transferred by syringe into the reaction vessel under argon. The reaction mixture was stirred at 60 °C for 2 hours, cooled to room temperature and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na_2SO_4), treated with 3-mercaptopropyl functionalized silica gel (Aldrich, 538086-100G) for 45 minutes, filtered and concentrated. Purification by chromatography (silica gel, 20-

CLAIMS:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof



(I)

wherein

R^x is hydrogen or C_1-C_3 alkyl;

R^y is C_1-C_3 alkyl, -(C_2-C_3 alkylenyl)-OH, or C_1-C_3 haloalkyl;

X^1 is N or CR^{x1} wherein

R^{x1} is hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, $-C(O)R^{dx1}$, $S(O)_2R^{dx1}$, $-S(O)_2NR^{bx1}R^{cx1}$, G^{x1}, C_1-C_6 haloalkyl, or C_1-C_6 alkyl; wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax1}, SR^{ax1}, $S(O)R^{dx1}$, $S(O)_2R^{dx1}$, $NR^{bx1}R^{cx1}$, $-C(O)R^{ax1}$, $-C(O)OR^{ax1}$, $-C(O)NR^{bx1}R^{cx1}$, $-S(O)_2NR^{bx1}R^{cx1}$, and G^{x1};

R^{ax1}, R^{bx1}, and R^{cx1}, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^a, or -(C_1-C_6 alkylenyl)-G^a;

R^{dx1}, at each occurrence, are each independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^a, or -(C_1-C_6 alkylenyl)-G^a;

X^2 is N or CR^{x2}; wherein

R^{x2} is hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-C(O)OR^{ax2}$, $-C(O)NR^{bx2}R^{cx2}$, $-C(O)R^{dx2}$, -C(O)H, $S(O)_2R^{dx2}$, $-S(O)_2NR^{bx2}R^{cx2}$, G^{x2}, C_1-C_6 haloalkyl, or C_1-C_6 alkyl; wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of OR^{ax2}, SR^{ax2}, $S(O)R^{dx2}$, $S(O)_2R^{dx2}$,

$NR^{bx2}R^{cx2}$, $-C(O)R^{ax2}$, $-C(O)OR^{ax2}$, $-C(O)NR^{bx2}R^{cx2}$, $-S(O)_2NR^{bx2}R^{cx2}$, and G^{x2};

R^{ax2}, R^{bx2}, and R^{cx2}, at each occurrence, are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^b, or -(C_1-C_6 alkylenyl)-G^b;

R^{dx2}, at each occurrence, is independently C_1-C_6 alkyl, C_1-C_6 haloalkyl, G^b, or -(C_1-C_6 alkylenyl)-G^b;

Y^1 is N or CR^u; wherein R^u is hydrogen, C_1-C_6 alkyl, halogen, or C_1-C_6 haloalkyl;

A^1 is N or CR^1, A^2 is N or CR^2, A^3 is N or CR^3; and A^4 is N or CR^4; with the proviso that zero, one, two, or three of A^1, A^2, A^3, and A^4 are N;

R^1, R^3, and R^4 are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, CN, or NO_2;

R^2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 haloalkyl, -CN, NO_2,
G^{2a}, $-OR^{2a}$, $-OC(O)R^{2d}$, $-OC(O)NR^{2b}R^{2c}$, $-SR^{2a}$, $-S(O)_2R^{2d}$, $-S(O)_2NR^{2b}R^{2c}$, $-C(O)R^{2d}$, $-C(O)OR^{2a}$, $-C(O)NR^{2b}R^{2c}$, $-NR^{2b}R^{2c}$, $-N(R^{2e})C(O)R^{2d}$, $-N(R^{2e})S(O)_2R^{2d}$, $-N(R^{2e})C(O)O(R^{2d})$, $-N(R^{2e})C(O)NR^{2b}R^{2c}$, $-N(R^{2e})S(O)_2NR^{2b}R^{2c}$, –($C_1$-$C_6$ alkylenyl)-G^{2a}, –(C_1-C_6 alkylenyl)-OR^{2a}, -(C_1-C_6 alkylenyl)-$OC(O)R^{2d}$, –(C_1-C_6 alkylenyl)-$OC(O)NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$S(O)_2R^{2d}$, -(C_1-C_6 alkylenyl)-$S(O)_2NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$C(O)R^{2d}$, –(C_1-C_6 alkylenyl)-$C(O)OR^{2a}$, -(C_1-C_6 alkylenyl)-$C(O)NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$NR^{2b}R^{2c}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)R^{2d}$, -(C_1-C_6 alkylenyl)-$N(R^{2e})S(O)_2R^{2d}$, –(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)O(R^{2a})$, –(C_1-C_6 alkylenyl)-$N(R^{2e})C(O)NR^{2b}R^{2c}$, –($C_1$-$C_6$ alkylenyl)-$N(R^{2e})S(O)_2NR^{2b}R^{2c}$, and –($C_1$-$C_6$ alkylenyl)-CN;

R^{2a}, R^{2b}, R^{2c}, and R^{2e}, at each occurrence, are each independently hydrogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, G^{2b}, or C_1-C_6 alkyl wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of $-OR^{z1}$, $NR^{z1}R^{z2}$, $-C(O)OR^{z1}$, $-C(O)NR^{z1}R^{z2}$, $-S(O)_2R^{z1}$, $-S(O)_2NR^{z1}R^{z2}$, and G^{2b};

R^{2d}, at each occurrence, is independently C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, G^{2b}, or C_1-C_6 alkyl wherein the C_1-C_6 alkyl is optionally substituted with one substituent selected from the group consisting of -OR^{z1}, $NR^{z1}R^{z2}$, $-C(O)OR^{z1}$, $-C(O)NR^{z1}R^{z2}$, $-S(O)_2R^{z1}$, $-S(O)_2NR^{z1}R^{z2}$, and G^{2b};

4-[2-(2,4-difluorophenoxy)-5-(morpholin-4-ylcarbonyl)phenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[4-(cyclohexyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(cyclopentyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-{4-[(4,4-difluorocyclohexyl)oxy]-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl}methanesulfonamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydro-2H-pyran-3-yloxy)phenyl]methanesulfonamide;

6-methyl-4-[2-(morpholin-4-ylcarbonyl)phenyl]-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(2,4,6-trifluorophenoxy)phenyl]ethanesulfonamide;

N-[4-(benzyloxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]methanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-2-fluoroethanesulfonamide;

N-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]-N'-methylsulfuric diamide;

N-[3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-4-(tetrahydrofuran-3-yloxy)phenyl]ethanesulfonamide;

methyl 6-methyl-7-oxo-4-(2-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

methyl 1,6-dimethyl-7-oxo-4-(2-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

ethyl 4-(5-amino-2-phenoxyphenyl)-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

6-methyl-4-(5-(methylsulfonamido)-2-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid;

ethyl 6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate;

N-ethyl-6-methyl-4-{5-[(methylsulfonyl)amino]-2-phenoxyphenyl}-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

4-[(cyclopropylmethyl)amino]-N-methyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

4-{2-[(2,2-difluorocyclopropyl)methoxy]-5-(ethylsulfonyl)phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(4-bromo-2-methoxyphenyl)-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-(2,4-difluorophenoxy)-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

4-{2-(cyclopropylmethoxy)-5-[(trifluoromethyl)sulfonyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{2-[(cyclopropylmethyl)amino]-5-[(trifluoromethyl)sulfonyl]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

6-[(cyclopropylmethyl)amino]-N,N-dimethyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

6-(2,4-difluorophenoxy)-N-methyl-5-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)pyridine-3-sulfonamide;

4-[2-(cyclopropylmethoxy)-6-methylphenyl]-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-{5-(ethylsulfonyl)-2-[(cis-4-methoxycyclohexyl)oxy]phenyl}-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

4-(cyclopropylmethoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

4-(cyclopropylmethoxy)-N-methyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzenesulfonamide;

N-[4-(cyclopropylmethoxy)-2-methyl-3-(6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)phenyl]ethanesulfonamide;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-N-ethyl-6-methyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-7-oxo-N-(2,2,2-trifluoroethyl)-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

4-[2-(2,4-difluorophenoxy)-5-(methylsulfonyl)phenyl]-6-methyl-2-(morpholin-4-ylcarbonyl)-1,6-dihydro-7H-pyrrolo[2,3-c]pyridin-7-one;

54. The compound of claim 53 or a pharmaceutically acceptable salt thereof, wherein A^1 is CR^1, A^2 is CR^2, A^3 is CR^3, and A^4 is CR^4.

55. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

56. Use of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer.

57. The use of claim 56 wherein the cancer is selected from the group consisting of: acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, glioblastoma, gliosarcoma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, leukemia, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, NUT midline carcinoma (NMC), non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma,