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(71) Applicant (for all designated States except US): **AMBIT BIOSCIENCES CORPORATION** [US/US]; 4215 Sorrento Valley Boulevard, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HADD, Michael, J.** [US/US]; 4215 Sorrento Valley Boulevard, San Diego, CA 92121 (US). **HOLLADAY, Mark, W.** [US/US]; 4215 Sorrento Valley Boulevard, San Diego, CA 92121 (US). **SETTI, Eduardo** [AR/US]; 804 North Delaware Street, San Mateo, CA 94401 (US).

(74) Agents: **RIEGER, Dale, L.** et al.; Jones Day, 222 East 41st Street, New York, NY 10017-6702 (US).

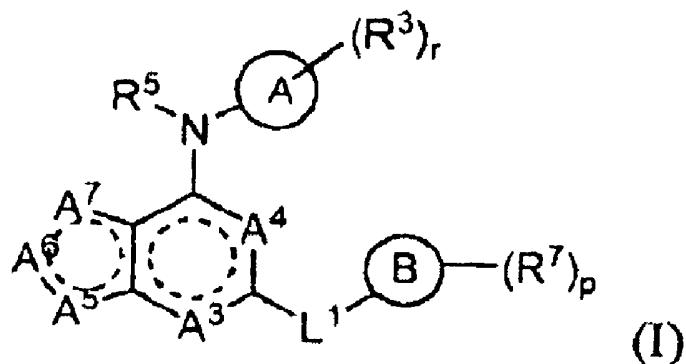
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(54) Title: THIENOPYRIDINE AND THIENOPYRIMIDINE COMPOUNDS AND METHODS OF USE THEREOF



(57) Abstract: Provided herein are thienopyridine and thienopyrimidine compounds of formula (I) for treatment of JAK kinase mediated diseases, including JAK2 kinase-, JAK3 kinase- or TYK2 kinase-mediated diseases. Also provided are pharmaceutical compositions comprising the compounds and methods of using the compounds and compositions.

THIENOPYRIDINE AND THIENOPYRIMIDINE COMPOUNDS AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of the priority of U.S. Provisional Application No. 61/379,301, filed September 1, 2010, the disclosure of which is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein are compounds that are modulators of JAK kinases, compositions comprising the compounds and methods of use thereof. The compounds provided are useful in the treatment, prevention, or amelioration of a disease or disorder related to JAK, including JAK2, JAK3 or TYK2 kinases, or one or more symptoms associated with such diseases or disorders. Further provided are methods for treatment of cancer, including blood borne and solid tumors.

BACKGROUND

[0003] The JAK kinase family is a cytoplasmic protein kinase family comprising the members JAK1, JAK2, JAK3 and TYK2. Growth factor or cytokine receptors that recruit JAK kinases include the interferon receptors, interleukin receptors (receptors for the cytokines IL-2 to IL-7, IL-9 to IL-13, IL-15, IL-23), various hormone receptors (erythropoietin (Epo) receptor, the thrombopoietin (Tpo) receptor, the leptin receptor, the insulin receptor, the prolactin (PRL) receptor, the Granulocyte Colony-Stimulating Factor (G-CSF) receptor and the growth hormone receptor, receptor protein tyrosine kinases (such as EGFR and PDGFR), and receptors for other growth factors such as leukemia inhibitory factor (LIF), Oncostatin M (OSM), IFN $\alpha/\beta/\gamma$, Granulocyte-macrophage colony-stimulating factor (GM-CSF), Ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1) (See, Rane, S.G. and Reddy E.P., *Oncogene* **2000** *19*, 5662-5679).

[0004] Phosphorylated receptors serve as docking sites for other SH-2 domain containing signaling molecules that interact with JAKs such as the STAT family of transcription factors, Src family of kinases, MAP kinases, PI3 kinase and protein tyrosine phosphatases (Rane S.G. and Reddy E.P., *Oncogene* **2000** *19*, 5662-5679). The family of latent cytoplasmic transcription factors, STATs, is the most well characterized downstream substrates for JAKs. The STAT proteins bind to phosphorylated cytokine receptors through their SH2 domains to become

phosphorylated by JAKs, which leads to their dimerization and release and eventual translocation to the nucleus where they activate gene transcription. The various members of STAT which have been identified thus far, are STAT1, STAT2, STAT3, STAT4, STAT5 (including STAT5a and STAT5b) and STAT6.

[0005] Since the JAK kinases may play an important signaling role via such receptors, disorders of fat metabolism, growth disorders and disorders of the immune system are all potential therapeutic targets.

[0006] The JAK kinases and JAK2 mutations are implicated in myeloproliferative disorders, cancers, including blood borne and solid tumors. Exemplary disorders include chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic eosinophilic leukemia (CEL), chronic myelomonocytic leukemia (CMML) and systemic mastocytosis (SM). Myeloproliferative disorders are believed to arise from either gain-of-function mutations to JAK itself or from activation by the oncprotein BCR-ABL, which specifically activates the JAK2 pathway. Several literature reports describe role of JAK2 mutations in various disorders. See, Samanta et al. *Cancer Res* **2006**, 66(13), 6468-6472, Sawyers et al. *Cell*, **1992**, 70, 901-910, Tefferi N. *Eng. J. Med.* (2007) 356(5): 444-445) Baxter et al. *Lancet* (2005) 365:1054-1056, Levine et al. *Blood* (2006, Jones et al. *Blood* (2005) 106:2162-2168) 107:4139-4141, Campbell et al. *Blood* (2006) 107(5): 2098-2100, Scott et al. *N Eng J Med* 2007 356(5): 459-468, Mercher et al. *Blood* (2006) 108(8): 2770-2778, Lacronique et al. *Science* (1997) 278:1309-1312, Lacronique et al. *Blood* (2000) 95:2535-2540, Griesinger F. et al. *Genes Chromosomes Cancer* (2005) 44:329-333, Bousquet et al. *Oncogene* (2005) 24:7248-7252, Schwaller et al. *Mol. Cell.* **2000** 6,693-704, and Zhao et al. *EMBO* **2002** 21(9), 2159-2167.

[0007] Literature indicates that JAK may also serve as a target for prostate cancer, including androgen-resistant prostate cancer. See, Barton et al. *Mol. Canc. Ther.* **2004** 3(1), 11-20, Blume-Jensen et al. *Nature* (2001) 411(6835):355-356 and Bromberg J *Clin Invest.* (2002) 109(9):1139-1142, Rane *Oncogene* (2000) 19(49):5662-5679. JAK as a prominent mediator of the cytokine signaling pathway, is considered to be a therapeutic target for inflammation and transplant rejections. See, Borie et al.,

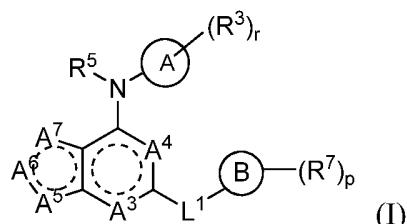
Transplantation (2005) 79(7):791-801 and Milici *et al.*, *Arthritis Research* (2008) 10(R14):1-9

[0008] Given the multitude of diseases attributed to the dysregulation of JAK signaling, many small molecule inhibitors of JAK are currently being developed. Examples of compounds in preclinical development include TG101209 (TargeGen). Examples of compounds being investigated in clinical studies include INCB018424 (Incyte), XL019 (Exelixis) and TG101348 (TargeGen). See, Pardanani *et al.* *Leukemia* 2007, 21:1658-1668; and Pardanai, A. *Leukemia* 2008 22:23-20.

[0009] There is, however, an ever-existing need to provide novel classes of compounds that are useful as inhibitors of enzymes in the JAK signaling pathway.

SUMMARY

[0010] Provided herein are compounds of formula (I)



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein

A is azoyl;

B is aryl or heteroaryl;

A³ and A⁴ are selected from N and CR^{6a}, such that at least one of A³ and A⁴ is

N;

A⁵, A⁶, and A⁷ are selected from S and CR⁶, such that one of A⁵, A⁶, or A⁷ is S and the others are CR⁶;

L¹ is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R¹ and R² are selected from (i), (ii), (iii), (iv) and (v) as follows:

(i) R¹ and R² together form =O, =S, =NR⁹ or =CR¹⁰R¹¹;

(ii) R¹ and R² are both -OR⁸, or R¹ and R², together with the carbon atom to which they are attached, form cycloalkyl or heterocyclyl wherein the cycloalkyl is substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one or two, substituents selected from halo, deuterio, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, =O, =N-OR²¹, -R^xOR²¹, -R^xN(R²²)₂, -R^xS(O)_qR²³, -C(O)R²¹, -C(O)OR²¹ and -C(O)N(R²²)₂ and

wherein the heterocyclyl contains one to two heteroatoms wherein each heteroatom is independently selected from O, NR²⁴, S, S(O) and S(O)₂;

(iii) R¹ is hydrogen or halo; and R² is halo;

(iv) R¹ is alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl is optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents selected from halo, cyano, alkyl, -R^xOR^w, -R^xS(O)_qR^v, -R^xNR^yR^z and -C(O)OR^w; and R² is hydrogen, halo or -OR⁸; and

(v) R¹ is halo, deuterio, -OR¹², -NR¹³R¹⁴, or -S(O)_qR¹⁵; and R² is hydrogen, deuterio, alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents selected from halo, cyano, alkyl, -R^xOR^w, -R^xS(O)_qR^v and -R^xNR^yR^z;

each R³ is independently hydrogen, deuterio, halo, alkyl, cyano, haloalkyl, deuteroaralkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy;

R⁵ is hydrogen or alkyl;

each R⁶ is independently selected from hydrogen, deuterio, halo, cyano, nitro, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -R^xOR¹⁸, -R^xNR¹⁹R²⁰, -R^xC(O)NR^yR^z, -R^xS(O)_qR^v, -R^xNR¹⁹C(O)R¹⁸, -R^xC(O)OR¹⁸ and -R^xNR¹⁹S(O)_qR^v; where the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl groups are each optionally substituted with one, two or three halo, oxo, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, haloalkyl, or cycloalkyl groups;

each R^{6a} is independently hydrogen, cyano or alkyl;

each R⁷ is independently halo, alkyl, haloalkyl or -R^xOR^w;

R⁸ is alkyl, alkenyl or alkynyl;

R⁹ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino;

R¹⁰ is hydrogen or alkyl;

R¹¹ is hydrogen, alkyl, haloalkyl or -C(O)OR⁸;

R¹² is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl,

heteroaralkyl, -C(O)R^v, -C(O)OR^w and -C(O)NR^yR^z, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R¹³ and R¹⁴ are selected as follows:

(i) R¹³ is hydrogen or alkyl; and R¹⁴ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy, -C(O)R^v, -C(O)OR^w, -C(O)NR^yR^z and -S(O)_qR^v, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio; or

(ii) R¹³ and R¹⁴, together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl wherein the heterocyclyl or heteroaryl are substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, alkyl, hydroxy, alkoxy, amino and alkylthio and wherein the heterocyclyl is optionally substituted with oxo;

R¹⁵ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -C(O)NR^yR^z or -NR^yR^z, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R¹⁸ is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R¹⁸ is optionally substituted with 1 to 3 groups Q¹, each Q¹ independently selected from alkyl, hydroxyl, halo, oxo, haloalkyl, alkoxy, aryloxy,

alkoxyalkyl, alkoxy carbonyl, alkoxy sulfonyl, carboxyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino;

R¹⁹ and R²⁰ are selected as follows:

(i) R¹⁹ and R²⁰ are each independently hydrogen or alkyl; or

(ii) R¹⁹ and R²⁰, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, oxo, alkyl, haloalkyl, hydroxyl and alkoxy;

R²¹ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl;

each R²² is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl; or both R²², together with the nitrogen atom to which they are attached, form a heterocyclyl optionally substituted with oxo;

R²³ is alkyl, alkenyl, alkynyl or haloalkyl;

R²⁴ is hydrogen or alkyl;

each R^x is independently alkylene, alkenylene, alkynylene or a direct bond;

R^y is hydrogen, alkyl, alkenyl or alkynyl;

R^w is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

R^y and R^z are selected as follows:

(i) R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl or heterocyclyl;

(ii) R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

r is 1-3;

p is 0-4; and

each q is independently 0, 1 or 2.

[0011] In certain embodiments, the compounds have activity as JAK kinase, including JAK2 kinase, modulators. The compounds are useful in medical treatments, pharmaceutical compositions and methods for modulating the activity of JAK kinase, including wildtype and/or mutated forms of JAK kinase. In certain embodiments, the

compounds provided herein have activity as JAK2 kinase modulators. In certain embodiments, the compounds are inhibitors of JAK kinase, including JAK2 kinase.

[0012] In one embodiment, the compounds for use in the compositions and methods provided herein are compounds of formula (I).

[0013] In one embodiment, the compound provided herein is a compound of formula (I). In one embodiment, the compound provided herein is a pharmaceutically acceptable salt of the compound of formula (I). In one embodiment, the compound provided herein is a solvate of the compound of formula (I). In one embodiment, the compound provided herein is a hydrate of compound of formula (I).

[0014] Also provided are pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable salts, solvates and hydrates thereof, and optionally comprising at least one pharmaceutical carrier.

[0015] Such pharmaceutical compositions deliver amounts effective for the treatment, prevention, or amelioration of diseases or disorders that include without limitation, myeloproliferative disorders such as polycythemia vera (PCV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic eosinophilic leukemia (CEL), chronic myelomonocytic leukemia (CMML), systemic mastocytosis (SM) and idiopathic myelofibrosis (IMF); leukemia such as myeloid leukemia including chronic myeloid leukemia (CML), imatinib-resistant forms of CML, acute myeloid leukemia (AML), and a subtype of AML, acute megakaryoblastic leukemia (AMKL); lymphoproliferative diseases such as myeloma; cancer such as cancer of the head and neck, prostate cancer, breast cancer, ovarian cancer, melanoma, lung cancers, brain tumors, pancreatic cancer and renal cancer; and inflammatory diseases or disorders related to immune dysfunction, immunodeficiency, immunomodulation, autoimmune diseases, tissue transplant rejection, graft-versus-host disease, wound healing, kidney disease, diabetic neuropathy, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, psoriasis, allergic rhinitis, inflammatory bowel disease including Crohn's disease and ulcerative colitis (UC), systemic lupus erythematosus (SLE), arthritis, osteoarthritis, rheumatoid arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease (COPD) and dry eye syndrome (or keratoconjunctivitis sicca

(KCS)). In one embodiment, such diseases or disorders are modulated or otherwise affected by the JAK kinases, including JAK2, JAK3 or TYK2.

[0016] Also provided herein are combination therapies using one or more compounds or compositions provided herein, or pharmaceutically acceptable salts, solvates or hydrates thereof, in combination with other pharmaceutically active agents for the treatment of the diseases and disorders described herein.

[0017] In one embodiment, such additional pharmaceutical agents include one or more chemotherapeutic agents, anti-proliferative agents, anti-inflammatory agents, immunomodulatory agents or immunosuppressive agents.

[0018] The compounds or compositions provided herein, or pharmaceutically acceptable salts, solvates or hydrates thereof, may be administered simultaneously with, prior to, or after administration of one or more of the above agents.

Pharmaceutical compositions containing a compound provided herein and one or more of the above agents are also provided.

[0019] In certain embodiments, provided herein are methods of treating, preventing or ameliorating a disease or disorder that is modulated or otherwise affected by JAK kinases, including JAK2 kinase such as wild type and/or mutant JAK2 kinase, or one or more symptoms or causes thereof. In another embodiment, provided herein are methods of treating, preventing or ameliorating a disease or disorder by modulating the JAK2 kinase selectively over JAK3 kinase. In yet another embodiment, provided herein are methods of treating, preventing or ameliorating a disease or disorder by modulating the JAK3 kinase selectively over JAK2 kinase. In another embodiment, provided herein are methods of treating, preventing or ameliorating a disease or disorder by modulating both JAK2 and JAK3. In one embodiment, provided are methods for treatment of cancer, including blood borne and solid tumors.

[0020] In practicing the methods, effective amounts of the compounds or compositions containing therapeutically effective concentrations of the compounds, which are formulated for systemic delivery, including parenteral, oral, or intravenous delivery, or for local or topical application are administered to an individual exhibiting the symptoms of the disease or disorder to be treated. The amounts are effective to ameliorate or eliminate one or more symptoms of the disease or disorder.

[0021] These and other aspects of the subject matter described herein will become evident upon reference to the following detailed description.

DETAILED DESCRIPTION

[0022] Provided herein are compounds of formula (I) that have activity as JAK kinase, including JAK2 kinase, modulators. Further provided are methods of treating, preventing or ameliorating diseases that are modulated by JAK kinases, including JAK2 kinase, and pharmaceutical compositions and dosage forms useful for such methods. The methods and compositions are described in detail in the sections below.

[0023] In certain embodiments, the compounds provided herein are JAK2 selective, *i.e.*, the compounds bind or interact with JAK2 at substantially lower concentrations than they bind or interact with other JAK receptors, including JAK3 receptor, at that same concentration. In certain embodiments, the compounds bind to JAK3 receptor at a binding constant at least about 3-fold higher, about 5-fold higher, about 10-fold higher, about 20-fold higher, about 25-fold higher, about 50-fold higher, about 75-fold higher, about 100-fold higher, about 200-fold higher, about 225-fold higher, about 250 fold higher, or about 300 fold higher than they bind JAK2 receptor.

[0024] In certain embodiments, the compounds provided herein are JAK3 selective, *i.e.*, the compounds bind or interact with JAK3 at substantially lower concentrations than they bind or interact with other JAK receptors, including JAK2 receptor, at that same concentration.

[0025] In certain embodiments, the compounds provided herein have Kd of greater than about 10 nM, 20 nM, 25 nM, 40 nM, 50 nM, or 70 nM against Aurora B kinase. Methods for determining binding constant against Aurora B kinase are known to one of skill in the art. Exemplary methods are described in US provisional application no. 61/294,413, and Fabian *et al.*, *Nature Biotechnology* **2005**, 23,329-336.

A. DEFINITIONS

[0026] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0027] “Alkyl” refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten, one to eight, one to six or one to four carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like.

[0028] “Alkenyl” refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing at least one double bond, in certain embodiment, having from 2 to 10 carbon atoms, from 2 to 8 carbon atoms, or from 2 to 6 carbon atoms, and which is attached to the rest of the molecule by a single bond or a double bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

[0029] “Alkynyl” refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms, and which is attached to the rest of the molecule by a single bond or a triple bond, *e.g.*, ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-3-ynyl and the like.

[0030] “Alkylene” and “alkylene chain” refer to a straight or branched divalent hydrocarbon chain consisting solely of carbon and hydrogen, containing no unsaturation and having from one to eight carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene and the like. The alkylene chain may be attached to the rest of the molecule through any two carbons within the chain.

[0031] “Alkoxy” refers to the group having the formula -OR wherein R is alkyl or haloalkyl, where the alkyl may be optionally substituted by one or more substituents, in one embodiment, one, two or three substituents independently selected from the group consisting of nitro, halo, hydroxyl, alkoxy, oxo, thioxo, amino, carbony, carboxy, azido, cyano, cycloalkyl, heteroaryl, and heterocyclyl.

[0032] “Alkoxyalkyl” refers to a group having the formula -R_hOR wherein R_h is a straight or branched alkylene chain and OR is alkoxy as defined above.

[0033] “Alkylthio” refers to a group having the formula -SR wherein R is alkyl or haloalkyl.

[0034] “aryloxy” refers to the group -OR, in which R is aryl, including lower aryl, such as phenyl.

[0035] “Amine” or “amino” refers to a group having the formula -NR’R” wherein R’ and R” are each independently hydrogen, alkyl, haloalkyl, hydroxyalkyl or alkoxyalkyl or wherein R’ and R”, together with the nitrogen atom to which they are attached form a heterocyclyl optionally substituted with halo, oxo, hydroxy or alkoxy.

[0036] “Aminoalkyl” refers to a group having the formula -R_hNR’R” wherein R_h is a straight or branched alkylene chain and wherein NR’R” is amino as defined above.

[0037] “Aminocarbonyl” refers to a group having the formula -C(O)NR’R” wherein -NR’R” is amino as defined above.

[0038] “Aryl” refers to a group of carbocyclic ring system, including monocyclic, bicyclic, tricyclic, tetracyclic C₆-C₁₈ ring systems, wherein at least one of the rings is aromatic. The aryl may be fully aromatic, examples of which are phenyl, naphthyl, anthracenyl, acenaphthylenyl, azulenyl, fluorenyl, indenyl and pyrenyl. The aryl may also contain an aromatic ring in combination with a non-aromatic ring, examples of which are acenaphene, indene, and fluorene. The term includes both substituted and unsubstituted moieties. The aryl group can be substituted with any described moiety, including, but not limited to, one or more moieties selected from the group consisting of halo (fluoro, chloro, bromo or iodo), alkyl, hydroxyl, amino, alkoxy, aryloxy, nitro and cyano.

[0039] “Cycloalkyl” refers to a stable monovalent monocyclic or bicyclic hydrocarbon group consisting solely of carbon and hydrogen atoms, having from three to ten carbon atoms, and which is saturated and attached to the rest of the molecule by a single bond, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decalinyl, norbornane, norbornene, adamantyl, bicyclo[2.2.2]octane and the like.

[0040] “Cycloalkylalkyl” refers to a group of the formula -R_aR_d where R_a is an alkyl group as defined above and R_d is a cycloalkyl group as defined above. The alkyl group and the cycloalkyl group may be optionally substituted as defined herein.

[0041] “Deutero” or “deuterium” refers to the hydrogen isotope deuterium having the chemical symbol D.

[0042] “Deuteroalkyl” refers to an isotopically enriched alkyl group in which one or more of the hydrogen atoms are replaced by deuterium.

[0043] “Halo”, “halogen” or “halide” refers to F, Cl, Br or I.

[0044] “Haloalkyl” refers to an alkyl group, in certain embodiments, C₁₋₆alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl, trifluoromethyl, 1-chloro-2-fluoroethyl, 2,2-difluoroethyl, 2-fluoropropyl, 2-fluoropropan-2-yl, 2,2,2-trifluoroethyl, 1,1-difluoroethyl, 1,3-difluoro-2-methylpropyl, 2,2-disfluorocyclopropyl, (trifluoromethyl)cyclopropyl, 4,4-disfluorocyclohexyl and 2,2,2-trifluoro-1,1-dimethyl-ethyl.

[0045] “Heterocyclyl” refers to a stable 3- to 15-membered ring group which consists of carbon atoms and from one to five heteroatoms selected from a group consisting of nitrogen, oxygen and sulfur. In one embodiment, the heterocyclic ring system group may be a monocyclic, bicyclic or tricyclic ring or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen or sulfur atoms in the heterocyclic ring system group may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl group may be partially or fully saturated or aromatic. The heterocyclic ring system may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Exemplary heterocyclic radicals include, azetidinyl, benzopyranonyl, benzopyranyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, chromanyl, chromonyl, coumarinyl, decahydroisoquinolinyl, dibenzofuranyl, dihydrobenzisothiazinyl, dihydrobenzisoxazinyl, dihydropyridinyl, dihydropyrazolyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4 dithianyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isochromanyl, isocoumarinyl, benzo[1,3]dioxol-5-yl, benzodioxolyl, 1,3-dioxolan-2-yl, dioxolanyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, tetrahydrofuran, oxazolidin-2-onyl, oxazolidinonyl, piperidinyl, piperazinyl, pyranyl, tetrahydrofuryl, tetrahydrofuran, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydrothienyl, pyrrolidinonyl, oxathiolanyl, and pyrrolidinyl.

[0046] “Heteroaryl” refers to a heterocyclyl group as defined above which is aromatic. The heteroaryl group may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound.

Examples of such heteroaryl groups include, but are not limited to: acridinyl, benzimidazolyl, benzindolyl, benzisoxazinyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, benzofuranyl, benzonaphthofuranyl, benzothiadiazolyl, benzothiazolyl, benzothiophenyl, benzotriazolyl, benzothiopyranyl, benzoxazinyl, benzoxazolyl, benzothiazolyl, β -carbolinyl, carbazolyl, cinnolinyl, dibenzofuranyl, furanyl, imidazolyl, imidazopyridinyl, imidazothiazolyl, indazolyl, indolizinyl, indolyl, isobenzothienyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, naphthyridinyl, octahydroindolyl, octahydroisoindolyl, oxazolidinonyl, oxazolidinyl, oxazolopyridinyl, oxazolyl, isoxazolyl, oxiranyl, perimidinyl, phenanthridinyl, phenathrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridopyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazinyl and triazolyl.

[0047] “Azolyl” refers to a 5-membered heterocyclic or heteroaryl ring system containing at least one nitrogen atom. Exemplary azolyl rings include pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, diazolyl, and triazolyl.

[0048] “Aralkyl” refers to a group of the formula -R_aR_b where R_a is an alkyl group as defined above, substituted by R_b, an aryl group, as defined above, *e.g.*, benzyl. Both the alkyl and aryl groups may be optionally substituted as defined herein.

[0049] “Heteroaralkyl” refers to a group of the formula -R_aR_f where R_a is an alkyl group as defined above and R_f is a heteroaryl group as defined herein. The alkyl group and the heteroaryl group may be optionally substituted as defined herein.

[0050] “Heterocyclalkyl” refers to a group of the formula -R_aR_e wherein R_a is an alkyl group as defined above and R_e is a heterocyclyl group as defined herein, where the alkyl group R_a may attach at either the carbon atom or the heteroatom of the heterocyclyl group R_e. The alkyl group and the heterocyclyl group may be optionally substituted as defined herein.

[0051] “Alkoxycarbonyl” refers to a group having the formula -C(O)OR in which R is alkyl, including lower alkyl.

- [0052] The term “dioxacycloalkyl” as used herein means a heterocyclic group containing two oxygen ring atoms and two or more carbon ring atoms.
- [0053] “Oxo” refers to the group =O attached to a carbon atom.
- [0054] “Thioalkyl” refers to a group having the formula –R_hSR_i where the R_h is a straight or branched alkylene chain and R_i is alkyl or haloalkyl.
- [0055] “Thioxo” refers to the group =S attached to a carbon atom.
- [0056] “IC₅₀” refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as cell growth or proliferation measured via any the *in vitro* or cell based assay described herein.
- [0057] Unless stated otherwise specifically described in the specification, it is understood that the substitution can occur on any atom of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl group.
- [0058] Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and inorganic salts, such as but not limited to, sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as hydrochlorides, hydrobromides, phosphate and sulfate; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates, mesylates, esylates, tosylates, besylates, trifluoroacetates, benzoates, fumarates, maleates, and oxalates.
- [0059] As used herein and unless otherwise indicated, the term “hydrate” means a compound provided herein or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.
- [0060] As used herein and unless otherwise indicated, the term “solvate” means a solvate formed from the association of one or more solvent molecules to a compound

provided herein. The term “solvate” includes hydrates (e.g., mono-hydrate, dihydrate, trihydrate, tetrahydrate and the like).

[0061] As used herein, “substantially pure” means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

[0062] Unless specifically stated otherwise, where a compound may assume alternative tautomeric, regiosomeric and/or stereoisomeric forms, all alternative isomers are intended to be encompassed within the scope of the claimed subject matter. For example, where a compound is described as having one of two tautomeric forms, it is intended that the both tautomers be encompassed herein. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures.

[0063] It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (*R*) or (*S*) configuration, or may be a mixture thereof.

[0064] Optically active (+) and (-), (*R*)- and (*S*)-, or (*D*)- and (*L*)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC or by crystallization.

[0065] As used herein, the term “enantiomerically pure” or “pure enantiomer” denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by

weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the desired enantiomer.

[0066] Where the number of any given substituent is not specified (*e.g.*, haloalkyl), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens.

[0067] In the description herein, if there is any discrepancy between a chemical name and chemical structure, the structure preferably controls.

[0068] As used herein, "isotopic composition" refers to the amount of each isotope present for a given atom, and "natural isotopic composition" refers to the naturally occurring isotopic composition or abundance for a given atom. Atoms containing their natural isotopic composition may also be referred to herein as "non-enriched" atoms. Unless otherwise designated, the atoms of the compounds recited herein are meant to represent any stable isotope of that atom. For example, unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural isotopic composition.

[0069] As used herein, "isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom.

[0070] As used herein, "isotopic enrichment" refers to the percentage of incorporation of an amount of a specific isotope at a given atom in a molecule in the place of that atom's natural isotopic abundance. For example, deuterium enrichment of 1% at a given position means that 1% of the molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The isotopic enrichment of the compounds provided herein can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[0071] In certain embodiments, compounds herein having one or more deutero substituents have an isotopic enrichment factor for each designated deuterium atom of from about 50% to about 99.5%, 60% to about 99.5%, 70% to about 99.5% deuterium incorporation.

[0072] In certain embodiments, compounds herein having one or more deutero substituents have an isotopic enrichment factor for each designated deuterium atom of at least about 3500 (about 52.5% deuterium incorporation), at least about 4000 (about 60% deuterium incorporation), at least about 4500 (about 67.5% deuterium incorporation), at least about 5000 (about 75% deuterium incorporation), at least about 5500 (82.5% deuterium incorporation), at least about 6000 (about 90% deuterium incorporation), at least about 6466.7 (about 97% deuterium incorporation), at least about 6600 (about 99% deuterium incorporation), or at least about 6633.3 (99.5% deuterium incorporation).

[0073] In certain embodiments, compounds herein having one or more deutero substituents have an isotopic enrichment factor for each designated deuterium atom of about 3500 (about 52.5% deuterium incorporation), about 4000 (about 60% deuterium incorporation), about 4500 (about 67.5% deuterium incorporation), about 5000 (about 75% deuterium incorporation), about 5500 (82.5% deuterium incorporation), about 6000 (about 90% deuterium incorporation), about 6466.7 (about 97% deuterium incorporation), about 6600 (about 99% deuterium incorporation), or about 6633.3 (99.5% deuterium incorporation).

[0074] “Anti-cancer agents” refers to anti-metabolites (e.g., 5-fluoro-uracil, methotrexate, fludarabine), antimicrotubule agents (e.g., vinca alkaloids such as vincristine, vinblastine; taxanes such as paclitaxel, docetaxel), alkylating agents (e.g., cyclophosphamide, melphalan, carmustine, nitrosoureas such as bischloroethylnitrosurea and hydroxyurea), platinum agents (e.g. cisplatin, carboplatin, oxaliplatin, JM-216 or satraplatin, CI-973), anthracyclines (e.g., doxorubicin, daunorubicin), antitumor antibiotics (e.g., mitomycin, idarubicin, adriamycin, daunomycin), topoisomerase inhibitors (e.g., etoposide, camptothecins), anti-angiogenesis agents (e.g. Sutent® and Bevacizumab) or any other cytotoxic agents, (estramustine phosphate, prednimustine), hormones or hormone agonists,

antagonists, partial agonists or partial antagonists, kinase inhibitors, and radiation treatment.

[0075] “Anti-inflammatory agents” refers to methotrexate, matrix metalloproteinase inhibitors, inhibitors of pro-inflammatory cytokines (e.g., anti-TNF molecules, TNF soluble receptors, and IL1) non-steroidal anti-inflammatory drugs (NSAIDs) such as prostaglandin synthase inhibitors (e.g., choline magnesium salicylate, salicylsalicyclic acid), COX-1 or COX-2 inhibitors), or glucocorticoid receptor agonists such as corticosteroids, methylprednisolone, prednisone, or cortisone.

[0076] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage or recognized abbreviations including abbreviations found in *J. Org. Chem.* 2007 72(1): 23A-24A or abbreviations established by the IUPAC-IUB Commission on Biochemical Nomenclature (see, *Biochem.* 1972, 11:942-944).

B. COMPOUNDS

[0077] In certain embodiments, provided herein are compounds of formula (I) or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein A is azolyl;

B is aryl or heteroaryl;

A³ and A⁴ are selected from N and CR^{6a}, such that at least one of A³ and A⁴ is N;

A⁵, A⁶, and A⁷ are selected from S and CR⁶, such that one of A⁵, A⁶, or A⁷ is S and the others are CR⁶;

L¹ is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R¹ and R² are selected from (i), (ii), (iii), (iv) and (v) as follows:

(i) R¹ and R² together form =O, =S, =NR⁹ or =CR¹⁰R¹¹;

(ii) R¹ and R² are both -OR⁸, or R¹ and R², together with the carbon atom to which they are attached, form cycloalkyl or heterocyclyl wherein the cycloalkyl is substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one or two, substituents selected from halo, deuterio, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, =O, =N-OR²¹, -R^xOR²¹, -R^xN(R²²)₂, -R^xS(O)_qR²³, -C(O)R²¹, -C(O)OR²¹ and -C(O)N(R²²)₂ and

wherein the heterocyclyl contains one to two heteroatoms wherein each heteroatom is independently selected from O, NR²⁴, S, S(O) and S(O)₂;

(iii) R¹ is hydrogen or halo; and R² is halo;

(iv) R¹ is alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl is optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substitutents selected from halo, cyano, alkyl, -R^xOR^w, -R^xS(O)_qR^v, -R^xNR^yR^z and -C(O)OR^w; and R² is hydrogen, halo or -OR⁸; and

(v) R¹ is halo, deutero, -OR¹², -NR¹³R¹⁴, or -S(O)_qR¹⁵; and R² is hydrogen, deutero, alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl is optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substitutents selected from halo, cyano, alkyl, -R^xOR^w, -R^xS(O)_qR^v and -R^xNR^yR^z;

each R³ is independently hydrogen, deutero, halo, alkyl, cyano, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy;

R⁵ is hydrogen or alkyl;

each R⁶ is independently selected from hydrogen, deutero, halo, cyano, nitro, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -R^xOR¹⁸, -R^xNR¹⁹R²⁰, -R^xC(O)NR^yR^z and -R^xS(O)_qR^v; where the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl groups are optionally substituted with one, two or three halo, oxo, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, haloalkyl, or cycloalkyl groups;

each R^{6a} is independently hydrogen, cyano or alkyl;

each R⁷ is independently halo, alkyl, haloalkyl or -R^xOR^w;

R⁸ is alkyl, alkenyl or alkynyl;

R⁹ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino;

R¹⁰ is hydrogen or alkyl;

R¹¹ is hydrogen, alkyl, haloalkyl or -C(O)OR⁸;

R¹² is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl,

heteroaralkyl, -C(O)R^v, -C(O)OR^w and -C(O)NR^yR^z, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R¹³ and R¹⁴ are selected as follows:

(i) R¹³ is hydrogen or alkyl; and R¹⁴ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy, -C(O)R^v, -C(O)OR^w, -C(O)NR^yR^z and -S(O)_qR^v, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio; or

(ii) R¹³ and R¹⁴, together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl wherein the heterocyclyl or heteroaryl are substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, alkyl, hydroxy, alkoxy, amino and alkylthio and wherein the heterocyclyl is optionally substituted with oxo;

R¹⁵ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -C(O)NR^yR^z or -NR^yR^z, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R¹⁸ is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R¹⁸ is optionally substituted with 1 to 3 groups Q¹, each Q¹ independently selected from alkyl, hydroxyl, halo, oxo, haloalkyl, alkoxy, aryloxy,

alkoxyalkyl, alkoxy carbonyl, alkoxy sulfonyl, carboxyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino;

R^{19} and R^{20} are selected as follows:

(i) R^{19} and R^{20} are each independently hydrogen or alkyl; or

(ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, oxo, alkyl, haloalkyl, hydroxyl and alkoxy;

R^{21} is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl;

each R^{22} is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl; or both R^{22} , together with the nitrogen atom to which they are attached, form a heterocyclyl optionally substituted with oxo;

R^{23} is alkyl, alkenyl, alkynyl or haloalkyl;

R^{24} is hydrogen or alkyl;

each R^x is independently alkylene, alkenylene, alkynylene or a direct bond;

R^y is hydrogen, alkyl, alkenyl or alkynyl;

R^w is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

R^y and R^z are selected as follows:

(i) R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or haloalkyl;

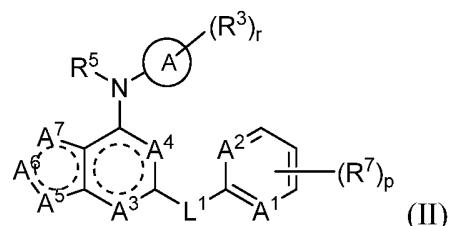
(ii) R^y and R^z , together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

r is 1-3;

p is 0-4; and

each q is independently 0, 1 or 2.

[0078] In certain embodiments, provided herein are compounds of formula (II)



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein

A is azolyl;

A¹ and A² are each independently selected from N and CR^{7a};

A³ and A⁴ are selected from N and CR^{6a}, such that at least one of A³ or A⁴ is N;

A⁵, A⁶, and A⁷ are selected from S and CR⁶, such that one of A⁵, A⁶, or A⁷ is S and the others are CR⁶;

L¹ is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R¹ and R² are selected from (i), (ii), (iii), (iv) and (v) as follows:

(i) R¹ and R² together form =O, =S, =NR⁹ or =CR¹⁰R¹¹;

(ii) R¹ and R² are both -OR⁸, or R¹ and R², together with the carbon atom to which they are attached, form dioxacycloalkyl;

(iii) R¹ is hydrogen or halo; and R² is halo;

(iv) R¹ is alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl is optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substitutents selected from halo, cyano, alkyl, -R^xOR^w, -R^xS(O)_qR^v, -R^xNR^yR^z and -C(O)OR^w; and R² is hydrogen, halo or -OR⁸; and

(v) R¹ is halo, deuterio, -OR¹², -NR¹³R¹⁴, or -S(O)_qR¹⁵; and R² is hydrogen, deuterio, alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substitutents selected from halo, cyano, alkyl, -R^xOR^w, -R^xS(O)_qR^v and -R^xNR^yR^z;

R³ is hydrogen, deuterio, halo, alkyl, cyano, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy;

R⁵ is hydrogen or alkyl;

each R⁶ is independently selected from hydrogen, deuterio, halo, cyano, nitro, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclalkyl, -R^xOR¹⁸, -R^xNR¹⁹R²⁰, -R^xC(O)NR^yR^z and -R^xS(O)_qR^v; where the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl groups are optionally substituted with

one, two or three halo, oxo, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, haloalkyl, or cycloalkyl groups;

each R^{6a} is independently hydrogen, cyano or alkyl;

each R⁷ is independently halo, alkyl, haloalkyl or -R^xOR^w;

R^{7a} is hydrogen or alkyl;

R⁸ is alkyl, alkenyl or alkynyl;

R⁹ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino;

R¹⁰ is hydrogen or alkyl;

R¹¹ is hydrogen, alkyl, haloalkyl or -C(O)OR⁸;

R¹² is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -C(O)R^v, -C(O)OR^w or -C(O)NR^yR^z, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R¹³ and R¹⁴ are selected as follows:

(i) R¹³ is hydrogen or alkyl; and R¹⁴ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy, -C(O)R^v, -C(O)OR^w, -C(O)NR^yR^z or -S(O)_qR^v, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio; or

(ii) R¹³ and R¹⁴, together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl wherein the heterocyclyl or heteroaryl are substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, alkyl, hydroxy, alkoxy, amino and alkylthio and wherein the heterocyclyl is optionally substituted with oxo;

R^{15} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-C(O)NR^yR^z$ or $-NR^yR^z$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R^{18} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{18} is optionally substituted with 1 to 3 groups Q^1 , each Q^1 independently alkyl, hydroxyl, halo, oxo, haloalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxy carbonyl, alkoxy sulfonyl, carboxyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl or amino;

R^{19} and R^{20} are selected as follows:

- (i) R^{19} and R^{20} are each independently hydrogen or alkyl; or
- (ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy; each R^x is independently alkylene or a direct bond;

R^v is hydrogen, alkyl, alkenyl or alkynyl;

R^w is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

R^y and R^z are selected as follows:

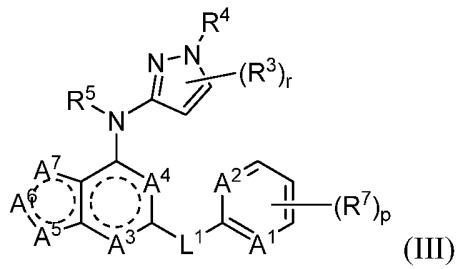
- (i) R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl or heterocyclyl;
- (ii) R^y and R^z , together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

r is 1-2;

p is 0-4; and

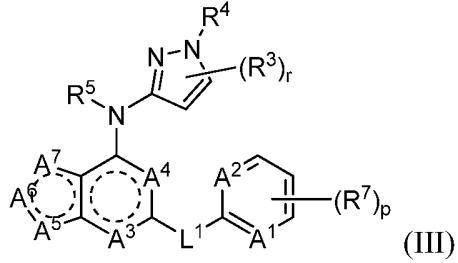
each q is independently 0, 1 or 2.

[0079] In certain embodiments, provided herein are compounds of formula (III)



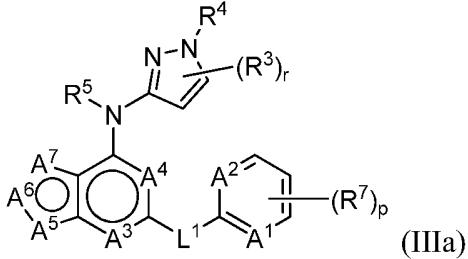
or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein R⁴ is hydrogen, alkyl or haloalkyl and the other variables are as described elsewhere herein.

[0080] In certain embodiments, provided herein are compounds of formula (III)



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein R⁴ is hydrogen, alkyl or haloalkyl and the other variables are as described elsewhere herein.

[0081] In certain embodiments, provided herein are compounds of formula (IIIa)



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein R⁴ is hydrogen, alkyl or haloalkyl and the other variables are as described elsewhere herein.

[0082] In certain embodiments, provided herein are compounds of formula (III) or (IIIa) or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein

A¹ and A² are each independently selected from N and CH;

A³ and A⁴ are selected from N and CR^{6a}, such that at least one of A³ or A⁴ is

N;

A⁵, A⁶, and A⁷ are selected from S and CR⁶, such that one of A⁵, A⁶, or A⁷ is S and the others are CR⁶;

L¹ is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R¹ and R² are selected from (i), (ii), (iii), (iv) and (v) as follows:

(i) R¹ and R² together form =O, =S, =NR⁹ or =CR¹⁰R¹¹;

(ii) R¹ and R² are both -OR⁸, or R¹ and R², together with the carbon atom to which they are attached, form cycloalkyl or heterocyclyl wherein the cycloalkyl is substituted with one or more, in one embodiment, one or two substituents selected from halo, deuterio, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, =O, =N-OR²¹, -R^xOR²¹, -R^xN(R²²)₂, -R^xS(O)_qR²³, -C(O)R²¹, -C(O)OR²¹ and -C(O)N(R²²)₂ and wherein the heterocyclyl contains one to two heteroatoms wherein each heteroatom is independently selected from O, NR²⁴, S, S(O) and S(O)₂;

(iii) R¹ is hydrogen or halo, and R² is halo;

(iv) R¹ is alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl are each optionally substituted with one or more substituents selected from halo, alkyl, -R^xOR^w, -R^xS(O)_qR^v and -R^xNR^yR^z and R² is hydrogen, halo and -OR⁸; and

(v) R¹ is halo, -OR¹², -NR¹³R¹⁴, -S(O)_qR¹⁵ or -R¹⁷C(O)OR¹², and R² is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl are each optionally substituted with one or more substituents selected from halo, alkyl, -R^xOR^w, -R^xS(O)_qR^v and -R^xNR^yR^z;

R³ is hydrogen, deuterio, deuteroalkyl, halo, alkyl, cyano, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy;

R⁴ is hydrogen, alkyl or haloalkyl

R⁵ is hydrogen or alkyl;

each R⁶ is independently hydrogen, deuterio, cyano, nitro, halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -R^xOR¹⁸, -R^xNR¹⁹R²⁰, or -R^xS(O)_qR^v;

each R^{6a} is independently hydrogen, cyano or alkyl;

each R⁷ is independently halo, alkyl, or haloalkyl;

R⁸ is alkyl, alkenyl or alkynyl;

R⁹ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino;

R¹⁰ is hydrogen or alkyl;

R¹¹ is hydrogen, alkyl, haloalkyl or -C(O)OR⁸;

R^{12} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-C(O)R^V$, $-C(O)OR^W$ or $-C(O)NR^YR^Z$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R^{13} and R^{14} are selected as follows:

(i) R^{13} is hydrogen or alkyl; and R^{14} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy, $-C(O)R^V$, $-C(O)OR^W$, $-C(O)NR^YR^Z$ or $-S(O)_qR^V$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio; or

(ii) R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form heterocyclyl or heteroaryl wherein the heterocyclyl or heteroaryl are substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, alkyl, hydroxy, alkoxy, amino and alkylthio and wherein the heterocyclyl is optionally substituted with oxo;

R^{15} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-C(O)NR^YR^Z$ or $-NR^YR^Z$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one, two or three, substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R^{18} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or

heteroarylalkyl; wherein R¹⁸ is optionally substituted with 1 to 3 groups Q¹, each Q¹ independently selected from alkyl, hydroxyl, halo, oxo, haloalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxycarbonyl, alkoxsulfonyl, carboxyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino;

R¹⁹ and R²⁰ are selected as follows:

(i) R¹⁹ and R²⁰ are each independently hydrogen or alkyl; or

(ii) R¹⁹ and R²⁰, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, oxo, alkyl, haloalkyl, hydroxyl and alkoxy;

R²¹ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl;

each R²² is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl; or both R²², together with the nitrogen atom to which they are attached, form a heterocyclyl optionally substituted with oxo;

R²³ is alkyl, alkenyl, alkynyl or haloalkyl;

R²⁴ is hydrogen or alkyl;

each R^x is independently alkylene, alkenylene, alkynylene or a direct bond;

R^v is hydrogen, alkyl, alkenyl or alkynyl;

R^w is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

R^y and R^z are selected as follows:

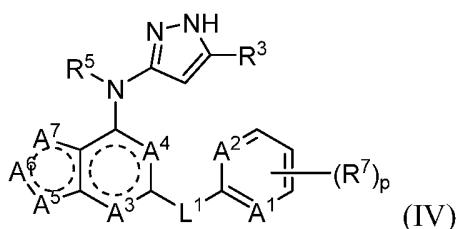
(i) R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl or heterocyclyl;

(ii) R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

p is 0-4; and

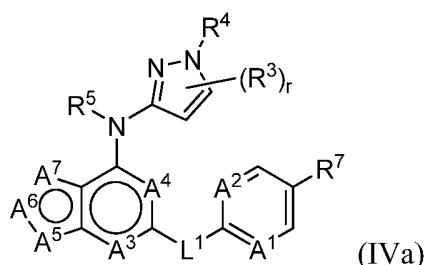
each q is independently 0, 1 or 2.

[0083] In certain embodiments, provided herein are compounds of formula (IV)



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

[0084] In certain embodiments, provided herein are compounds of formula (IVa)



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

[0085] In certain embodiments, provided herein are compounds of formula (IV) or (IVa) or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein

A¹ and A² are each independently selected from N and CH;

A³ and A⁴ are selected from N and CR^{6a}, such that at least one of A³ or A⁴ is N;

A⁵, A⁶, and A⁷ are selected from S and CR⁶, such that one of A⁵, A⁶, or A⁷ is S and the others are CR⁶;

L¹ is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R¹ and R² are selected as follows:

(i) R¹ and R² together form =O;

(ii) R¹ is hydrogen or halo; and R² is halo;

(iii) R¹ is alkyl, and R² is hydrogen, alkyl, halo, hydroxy or alkoxy; or

(iv) R¹ is halo, hydroxy or alkoxy; and R² is hydrogen or alkyl;

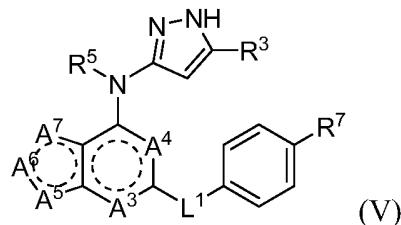
R³ is hydrogen, deutero, halo, alkyl, deutoalkyl, cyano, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy;

R⁵ is hydrogen or alkyl;

each R⁶ is independently hydrogen, deuterio, halo, alkyl, haloalkyl, alkoxy or haloalkoxy;

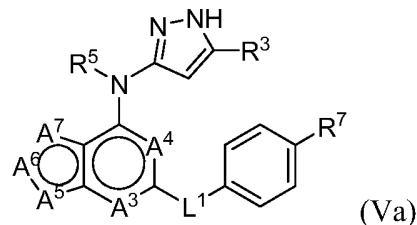
each R^{6a} is independently hydrogen, cyano or alkyl;
 each R⁷ is independently halo, alkyl, or haloalkyl; and
 p is 1 or 2.

[0086] In certain embodiments, provided herein are compounds of formula (V)



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

[0087] In certain embodiments, provided herein are compounds of formula (Va)



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein.

[0088] In certain embodiments, provided herein are compounds of formula (V) or (Va) pharmaceutically acceptable salts, solvates or hydrates thereof, wherein

A³ and A⁴ are selected from N and CR^{6a}, such that at least one of A³ or A⁴ is N;

A⁵, A⁶, and A⁷ are selected from S and CR⁶, such that one of A⁵, A⁶, or A⁷ is S and the others are CR⁶;

L¹ is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R¹ and R² are selected as follows:

- (i) R¹ and R² together form =O;
- (ii) R¹ is hydrogen or halo; and R² is halo;
- (iii) R¹ is alkyl, and R² is hydrogen, alkyl, halo, hydroxy or alkoxy; or
- (iv) R¹ is halo, hydroxy or alkoxy; and R² is hydrogen or alkyl;

R³ is hydrogen, alkyl or cycloalkyl,

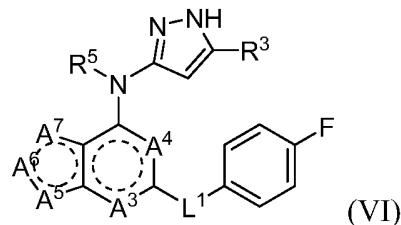
R⁵ is hydrogen or alkyl;

R^6 hydrogen, halo or alkyl;

R^{6a} is hydrogen or alkyl; and

R^7 is halo.

[0089] In certain embodiments, provided herein are compounds of formula (VI)



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein. In certain embodiments, provided herein are compounds of formula (VI) or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein

A^3 and A^4 are selected from N and CR^{6a}, such that at least one of A^3 or A^4 is

N;

A^5 , A^6 , and A^7 are selected from S and CR⁶, such that one of A^5 , A^6 , or A^7 is S and the others are CR⁶;

L^1 is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R^1 and R^2 are selected as follows:

(i) R^1 and R^2 together form =O;

(ii) R^1 is hydrogen or halo; and R^2 is halo;

(iii) R^1 is alkyl, and R^2 is hydrogen, alkyl, halo, hydroxy or alkoxy; or

(iv) R^1 is halo, hydroxy or alkoxy; and R^2 is hydrogen or alkyl;

R^6 is hydrogen, halo or alkyl; and

each R^{6a} is hydrogen or alkyl.

[0090] In certain embodiments, A^5 , A^6 , and A^7 are selected from (i), (ii) and (iii):

(i) A^5 is S, A^6 is CR⁶ where R⁶ is H, alkyl, haloalkyl or cycloalkyl and A^7 is CH;

(ii) A^5 is CH, A^6 is S and A^7 is CH;

(iii) A^5 is CR⁶ where R⁶ is H, alkyl, haloalkyl or cycloalkyl, A^6 is CR⁶ where R⁶ is H, alkyl, haloalkyl or cycloalkyl and A^7 is S. In another embodiment, R⁶ is H or alkyl.

[0091] In certain embodiments, R^6 is H.

[0092] In certain embodiments, L^1 is -C(R¹)(R²)-, -S(O)- or -S(O)₂-; and

R^1 and R^2 are selected as follows:

- (i) R¹ and R² together form =O or dioxacycloalkyl;
- (ii) R¹ is hydrogen or halo; and R² is halo;
- (iii) R¹ is alkyl, and R² is hydrogen, alkyl, halo, hydroxyl, alkoxy or amino; and
- (iv) R¹ is halo, hydroxyl, alkoxy or amino; and R² is hydrogen.

[0093] In certain embodiments, L¹ is -C(R¹)(R²)-, -S(O)- or -S(O)₂-; and R¹ and R² are selected as follows:

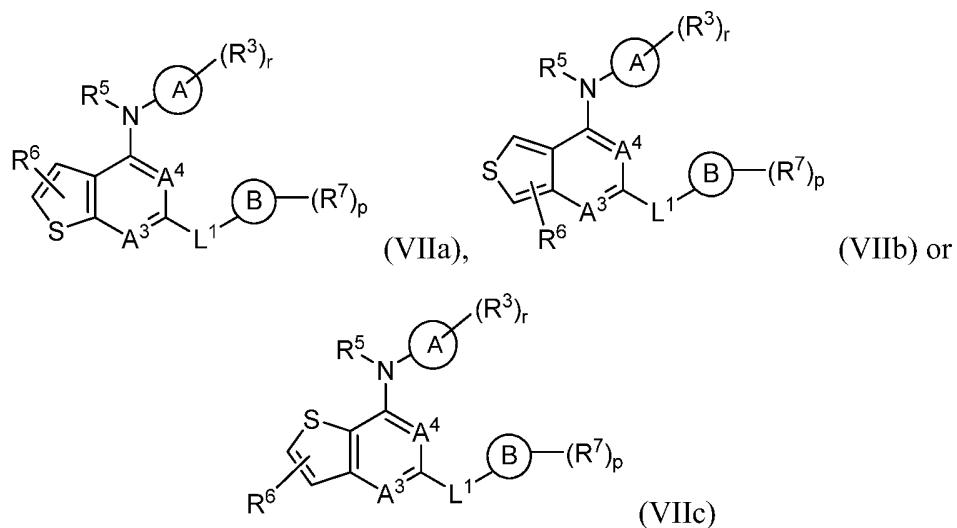
- (i) R¹ is hydrogen or halo; and R² is halo;
- (ii) R¹ is alkyl, and R² is hydrogen, alkyl, halo, hydroxyl, alkoxy or amino; and
- (iii) R¹ is halo, hydroxyl, alkoxy or amino; and R² is hydrogen.

[0094] In certain embodiments, when A⁵ and A⁶ are both CR⁶ where at least one R⁶ is alkyl, and A⁷ is S, then when L¹ is -C(R¹)(R²)-, R¹ and R² together do not form =O. In certain embodiments, when A⁵ and A⁶ are both CR⁶ where at least one R⁶ is alkyl, haloalkyl or cycloalkyl, and A⁷ is S, then when L¹ is -C(R¹)(R²)-, R¹ and R² together do not form =O. In certain embodiments, A⁵ and A⁶ are both CR⁶ where at least one R⁶ is alkyl, haloalkyl or cycloalkyl, and A⁷ is S; L¹ is -C(R¹)(R²)-, -S(O)- or -S(O)₂-; and

R¹ and R² are selected as follows:

- (i) R¹ is hydrogen or halo; and R² is halo;
- (ii) R¹ is alkyl, and R² is hydrogen, alkyl, halo, hydroxyl, alkoxy or amino; and
- (iii) R¹ is halo, hydroxyl, alkoxy or amino; and R² is hydrogen.

[0095] In certain embodiments, provided herein are compounds of formula (VIIa), (VIIb) or (VIIc):



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein. In certain embodiments, provided herein are compounds of formula (VIIa), (VIIb) or (VIIc), wherein A is pyrazolyl, imidazolyl, or thiazolyl; B is phenyl, pyridinyl or pyrimidinyl, and the other variables are as described herein. In certain embodiments, provided herein are compounds of formula (VIIa), (VIIb) or (VIIc), wherein

A is azolyl;

B is phenyl, pyridinyl or pyrimidinyl;

A^3 and A^4 are selected from N and CR^{6a}, such that at least one of A^3 or A^4 is N;

L^1 is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R¹ and R² are selected as follows:

- (i) R¹ and R² together form =O;
- (ii) R¹ is hydrogen or halo; and R² is halo;
- (iii) R¹ is alkyl, and R² is hydrogen, alkyl, halo, hydroxy or alkoxy; or
- (iv) R¹ is halo, hydroxy or alkoxy; and R² is hydrogen or alkyl;

R³ is hydrogen, alkyl, deuteroalkyl or cycloalkyl;

R⁵ is hydrogen or alkyl;

R⁶ is hydrogen, halo, cyano, alkyl, or haloalkyl;

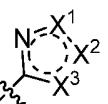
each R^{6a} is independently hydrogen or alkyl;

each R⁷ is independently halo, alkyl, haloalkyl or alkoxy;

p is 0-2; and

r is 0-2.

[0096] In one embodiment, A is pyrazolyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, or triazolyl. In one embodiment, A is pyrazolyl. In one embodiment, A is imidazolyl.



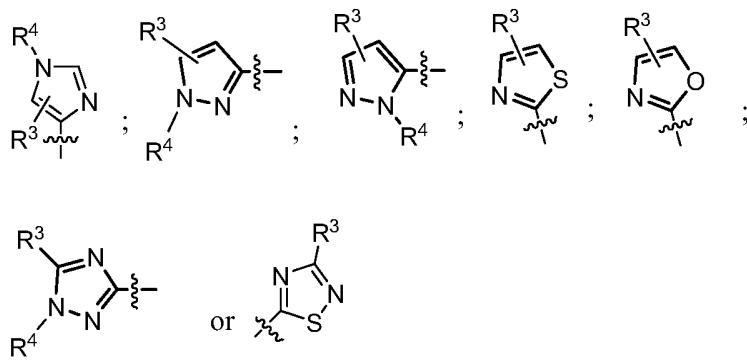
[0097] In one embodiment, A is ,

wherein X^1 , X^2 and X^3 are selected from (i) through (vi) as follows

- (i) X^1 is NR⁴, X^2 is CR³ and X^3 is CH;
 - (ii) X^1 is CR³, X^2 is NR⁴ and X^3 is CH;
 - (iii) X^1 is CR³, X^2 is NR⁴ and X^3 is S;
 - (iv) X^1 is CR³, X^2 is NR⁴ and X^3 is N;
 - (v) X^1 is CR³, X^2 is S or O and X^3 is CR³; and
 - (vi) X^1 is CR³, X^2 is CR³ and X^3 is S or O;

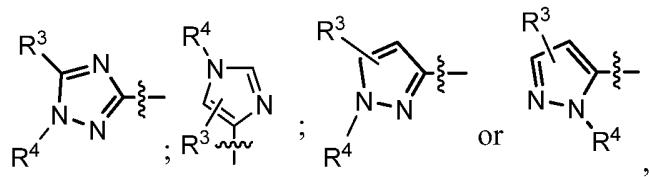
and the other variables are as described elsewhere herein.

[0098] In one embodiment, A is

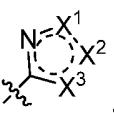


wherein each R³ is independently hydrogen, halo, alkyl, cyano, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy; and each R⁴ is independently hydrogen, or alkyl.

[0099] In one embodiment, A is



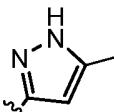
wherein each R³ is independently hydrogen, halo, alkyl, hydroxy or alkoxy; and each R⁴ is independently hydrogen, or alkyl.



[00100] In one embodiment, A is , wherein X¹, X² and X³ are selected from (i) and (ii) as follows:

- (i) X¹ is NR⁴, X² is CR³ and X³ is CH; and
- (ii) X¹ is CH, X² is CR³ and X³ is S,

and the other variables are as described elsewhere herein.



[00101] In one embodiment, A is .

[00102] In one embodiment, A¹ is CH and A² is N. In one embodiment, A¹ is N and A² is CH. In one embodiment, A¹ is N and A² is N.

[00103] In one embodiment, R¹ and R² together form =O.

[00104] In one embodiment, R¹ and R², together with the carbon atom to which they are attached, form cycloalkyl or heterocyclyl wherein the cycloalkyl is substituted with one or more, in one embodiment, one to four, in one embodiment, one to three, in one embodiment, one or two, substituents selected from halo, deutero, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, =O, =N-OR²¹, -R^xOR²¹, -R^xN(R²²)₂, -R^xS(O)_qR²³, -C(O)R²¹, -C(O)OR²¹ and -C(O)N(R²²)₂ and wherein the heterocyclyl contains one or two heteroatoms each independently selected from O, NR²⁴, S, S(O) and S(O)₂. In one embodiment, R¹ and R², together with the carbon atom to which they are attached, form dioxacycloalkyl.

[00105] In one embodiment, R¹ and R² are both halo. In one embodiment, R¹ and R² are both fluoro.

[00106] In one embodiment, R¹ is hydroxy or alkoxy, and R² is hydrogen or alkyl. In one embodiment, R¹ is hydroxy, and R² is hydrogen or methyl.

[00107] In one embodiment, R³ is hydrogen or alkyl. In another embodiment, R³ is hydrogen or methyl. In another embodiment, R³ is hydrogen. In one embodiment, R⁴ is hydrogen. In one embodiment, R⁵ is hydrogen.

[00108] In one embodiment, each R⁶ is independently selected from hydrogen, deutero, halo, cyano, nitro, alkyl, alkenyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, alkoxy, aryl, haloaryl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxy, -R^xOR¹⁸, -R^xNR¹⁹R²⁰, -R^xC(O)NR^yR^z, -R^xS(O)_qR^v, -R^xNR¹⁹C(O)R¹⁸, -R^xC(O)OR¹⁸

and $-R^xNR^{19}S(O)_qR^v$ where R^{18} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{18} is optionally substituted with 1 to 3 groups Q^1 , each Q^1 independently selected from alkyl, hydroxyl, halo, oxo, haloalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxy carbonyl, alkoxy sulfonyl, carboxyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino; R^x is independently alkylene or a direct bond; R^v is hydrogen, or alkyl; R^y and R^z are each independently hydrogen or alkyl; and R^{19} and R^{20} are selected as follows:

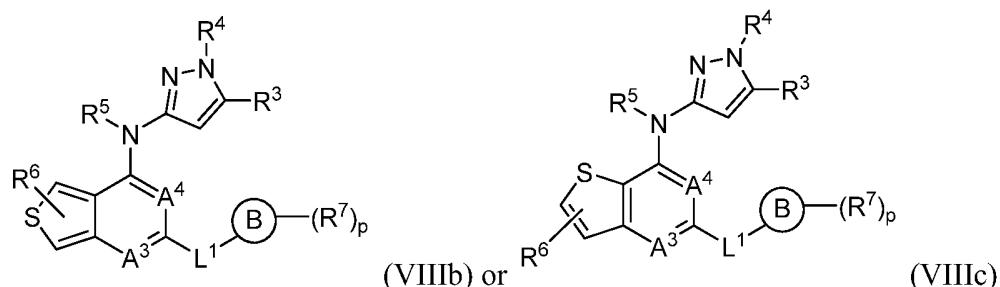
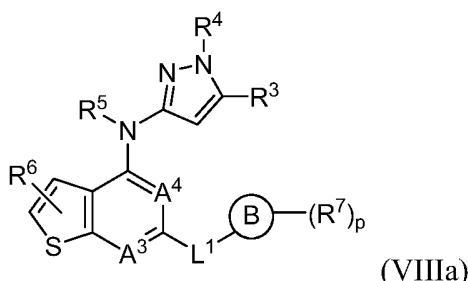
- (i) R^{19} and R^{20} are each independently hydrogen or alkyl; or
- (ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, oxo, alkyl, haloalkyl, hydroxyl and alkoxy.

[00109] In one embodiment, each R^6 is independently hydrogen, deuterio, halo, cyano, nitro, alkyl, alkenyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, alkoxy, aryl, haloaryl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxy, $-R^xOR^{18}$, $-R^xNR^{19}R^{20}$, $-R^xC(O)NR^yR^z$ or $-R^xS(O)_qR^v$, where R^{18} is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R^{18} is optionally substituted with 1 to 3 groups Q^1 , each Q^1 independently selected from alkyl, hydroxyl, halo, oxo, haloalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxy carbonyl, alkoxy sulfonyl, carboxyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloaryl and amino; R^x is independently alkylene or a direct bond; R^v is hydrogen, or alkyl; R^y and R^z are each independently hydrogen or alkyl; and R^{19} and R^{20} are selected as follows:

- (i) R^{19} and R^{20} are each independently hydrogen or alkyl; or
- (ii) R^{19} and R^{20} , together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, oxo, alkyl, haloalkyl, hydroxyl and alkoxy.

[00110] In one embodiment, each R^6 is independently hydrogen, deuterio, cyano, halo, alkyl, alkoxy, haloalkoxy or cycloalkyl.

- [00111] In one embodiment, each R⁶ is independently hydrogen, methyl or *tert*-butyl.
 - [00112] In one embodiment, each R^{6a} is hydrogen.
 - [00113] In one embodiment, R⁷ is halo. In one embodiment, R⁷ is fluoro.
 - [00114] In one embodiment, p is 1 or 2. In one embodiment, p is 1.
 - [00115] In certain embodiments, provided herein are compounds of formula (VIIIa), (VIIIb) or (VIIIc):



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein. In certain embodiments, provided herein are compounds of formula (VIIIa), (VIIIb) or (VIIIc), wherein B is phenyl, pyridinyl or pyrimidinyl, and the other variables are as described elsewhere herein. In certain embodiments, provided herein are compounds of formula (VIIIa), (VIIIb) or (VIIIc), wherein

B is phenyl, pyridinyl or pyrimidinyl;

A^3 and A^4 are selected from N and CH, such that at least one of A^3 or A^4 is N;

L¹ is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R^1 and R^2 are selected from (i), (ii), (iii) and (iv) as follows:

- (i) R^1 and R^2 together form =O;
 - (ii) R^1 is hydrogen or halo; and R^2 is halo;
 - (iii) R^1 is alkyl, and R^2 is hydrogen, alkyl, halo, hydroxy or alkoxy; or
 - (iv) R^1 is halo, hydroxy or alkoxy; and R^2 is hydrogen or alkyl;

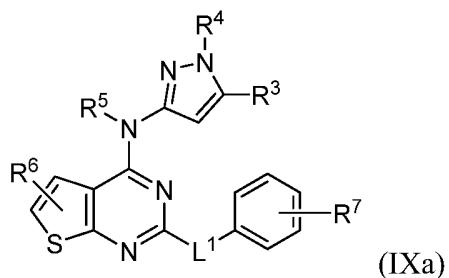
R^3 is alkyl, haloalkyl, deuteroalkyl or cycloalkyl;
 R^4 is hydrogen or alkyl;
 R^5 is hydrogen or alkyl;
 R^6 is hydrogen, deuterio, halo, cyano, alkyl, haloalkyl, alkoxy or haloalkoxy;
each R^7 is independently halo, alkyl, haloalkyl or alkoxy; and
 p is 0-2.

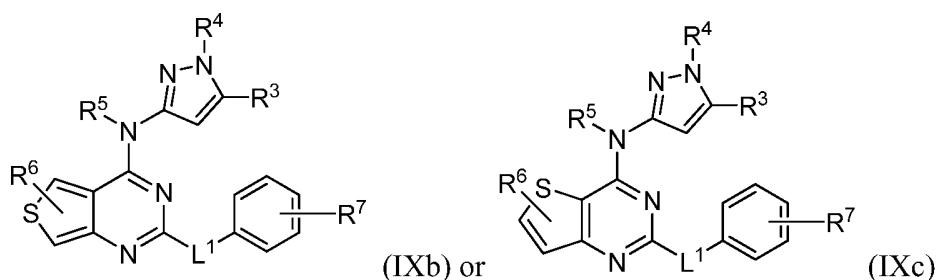
In certain embodiments, provided herein are compounds of formula (VIIIa), (VIIIb) or (VIIIc), wherein

B is phenyl, pyridinyl or pyrimidinyl;
 A^3 and A^4 are selected from N and CH, such that at least one of A^3 or A^4 is N;
 L^1 is $-C(R^1)(R^2)-$, $-S(O)-$ or $-S(O)_2-$;
 R^1 and R^2 are selected from (i), (ii), (iii) and (iv) as follows:
(i) R^1 and R^2 together form =O;
(ii) R^1 is hydrogen or halo; and R^2 is halo;
(iii) R^1 is alkyl, and R^2 is hydrogen, alkyl, halo, hydroxy or alkoxy; or
(iv) R^1 is halo, hydroxy or alkoxy; and R^2 is hydrogen or alkyl;

R^3 is hydrogen, alkyl or cycloalkyl,
 R^4 is hydrogen or alkyl;
 R^5 is hydrogen or alkyl;
 R^6 is hydrogen, deuterio, halo, cyano, alkyl, haloalkyl, alkoxy or haloalkoxy;
each R^7 is independently halo, alkyl, haloalkyl or alkoxy; and
 p is 0-2.

[00116] In certain embodiments, provided herein are compounds of formula (IXa), (IXb) or (IXc):





or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein

B is phenyl, pyridinyl or pyrimidinyl;

L^1 is $-C(R^1)(R^2)-$, $-S(O)-$ or $-S(O)_2-$;

R^1 and R^2 are selected from (i), (ii), (iii) and (iv) as follows:

- (i) R^1 and R^2 together form =O;
 - (ii) R^1 is hydrogen or halo; and R^2 is halo;
 - (iii) R^1 is alkyl, and R^2 is hydrogen, alkyl, halo, hydroxy or alkoxy; or
 - (iv) R^1 is halo, hydroxy or alkoxy; and R^2 is hydrogen or alkyl;

R^3 is hydrogen, alkyl, deuteroalkyl or cycloalkyl,

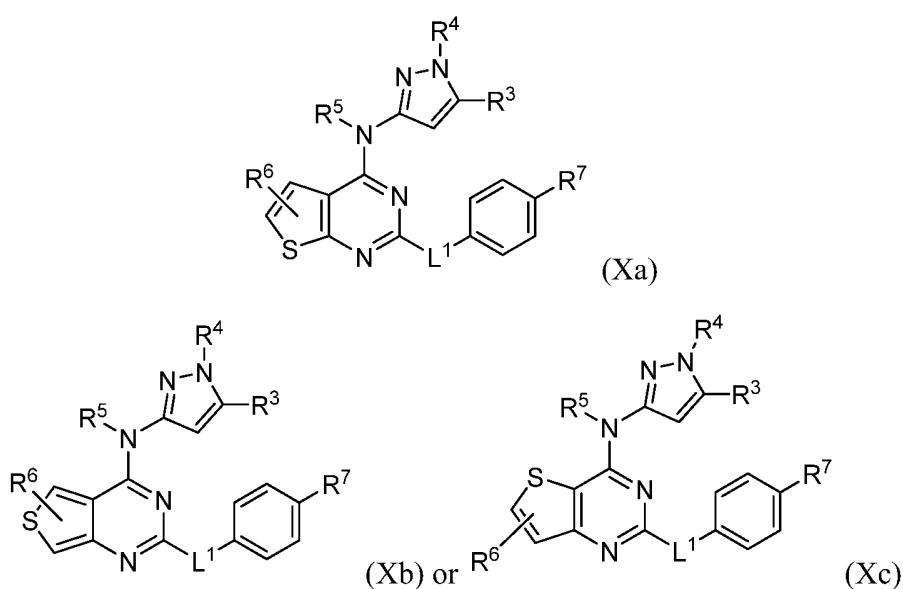
R⁴ is hydrogen or alkyl;

R⁵ is hydrogen or alkyl;

R^6 is hydrogen, deutero, halo, cyano, alkyl, or haloalkyl; and

each R⁷ is independently halo, alkyl, haloalkyl or alkoxy.

[00117] In certain embodiments, provided herein are compounds of formula (Xa), (Xb) or (Xc):



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein the variables are as described elsewhere herein. In certain embodiments, provided herein are compounds of formula (Xa), (Xb) or (Xc), wherein

L¹ is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R¹ and R² are selected from (i), (ii), (iii) and (iv) as follows:

(i) R¹ and R² together form =O;

(ii) R¹ is hydrogen or halo; and R² is halo;

(iii) R¹ is alkyl, and R² is hydrogen, alkyl, halo, hydroxy or alkoxy; or

(iv) R¹ is halo, hydroxy or alkoxy; and R² is hydrogen or alkyl;

R³ is hydrogen, alkyl, deuteroalkyl or cycloalkyl,

R⁵ is hydrogen or alkyl;

R⁴ is hydrogen or alkyl;

R⁶ hydrogen, halo, cyano, alkyl, or haloalkyl;

each R⁷ is halo.

[00118] In one embodiment, provided herein is a compound selected from 2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine;

2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine;

(4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanone;

(4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanol;

(4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanone;

(4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanol;

2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine;

2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine;

2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine;
2-(difluoro(4-fluorophenyl)methyl)-6-methyl-N-(5-methyl-1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine;
2-(difluoro(4-fluorophenyl)methyl)-6-methyl-N-(1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine;
(4-fluorophenyl)(6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanol;
(4-fluorophenyl)(6-methyl-4-((1-methyl-1H-imidazol-4-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanol;
(4-((1H-pyrazol-3-yl)amino)-6-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanol;
(4-fluorophenyl)(6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanone;
(4-fluorophenyl)(7-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanone;
(4-fluorophenyl)(7-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanol;
(4-((1H-pyrazol-3-yl)amino)-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone;
(4-((1H-pyrazol-3-yl)amino)-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol;
(6-(tert-butyl)-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone;
(4-((1H-pyrazol-3-yl)amino)-6-(tert-butyl)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone;
(4-fluorophenyl)(6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanol;
(6-(tert-butyl)-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol;
(4-((1H-pyrazol-3-yl)amino)-6-(tert-butyl)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol;

2-(difluoro(4-fluorophenyl)methyl)-6-ethyl-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine compound with propane (1:1);
2-(difluoro(4-fluorophenyl)methyl)-6-ethyl-N-(1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine compound with propane (1:1);
(4-fluorophenyl)(5-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanone;
(4-((1H-pyrazol-3-yl)amino)-5-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone;
(4-fluorophenyl)(5-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanol;
(4-((1H-pyrazol-3-yl)amino)-5-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanol;
1-(4-fluorophenyl)-1-(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)ethanol;
2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine;
(4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,4-d]pyrimidin-2-yl)methanol;
2-(4-fluorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine;
and
2-(difluoro(5-fluoropyridin-2-yl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine;
or pharmaceutically acceptable salts, solvates or hydrates thereof.

[00119] Also provided herein are isotopically enriched analogs of the compounds provided herein. Isotopic enrichment (for example, deuteration) of pharmaceuticals to improve pharmacokinetics (“PK”), pharmacodynamics (“PD”), and toxicity profiles, has been demonstrated previously with some classes of drugs. See, for example, Lijinsky *et. al.*, *Food Cosmet. Toxicol.*, 20: 393 (1982); Lijinsky *et. al.*, *J. Nat. Cancer Inst.*, 69: 1127 (1982); Mangold *et. al.*, *Mutation Res.* 308: 33 (1994); Gordon *et. al.*, *Drug Metab. Dispos.*, 15: 589 (1987); Zello *et. al.*, *Metabolism*, 43: 487 (1994); Gately *et. al.*, *J. Nucl. Med.*, 27: 388 (1986); Wade D, *Chem. Biol. Interact.* 117: 191 (1999).

[00120] Isotopic enrichment of a drug can be used, for example, to (1) reduce or eliminate unwanted metabolites, (2) increase the half-life of the parent drug, (3) decrease the number of doses needed to achieve a desired effect, (4) decrease the amount of a dose necessary to achieve a desired effect, (5) increase the formation of active metabolites, if any are formed, and/or (6) decrease the production of deleterious metabolites in specific tissues and/or create a more effective drug and/or a safer drug for combination therapy, whether the combination therapy is intentional or not.

[00121] Replacement of an atom for one of its isotopes often will result in a change in the reaction rate of a chemical reaction. This phenomenon is known as the Kinetic Isotope Effect (“KIE”). For example, if a C–H bond is broken during a rate-determining step in a chemical reaction (*i.e.* the step with the highest transition state energy), substitution of a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect (“DKIE”). (*See, e.g.*, Foster *et al.*, *Adv. Drug Res.*, vol. 14, pp. 1-36 (1985); Kushner *et al.*, *Can. J. Physiol. Pharmacol.*, vol. 77, pp. 79-88 (1999)).

[00122] Tritium (“T”) is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T₂O. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level. Substitution of tritium (“T”) for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects. Similarly, substitution of isotopes for other elements, including, but not limited to, ¹³C or ¹⁴C for carbon, ³³S, ³⁴S, or ³⁶S for sulfur, ¹⁵N for nitrogen, and ¹⁷O or ¹⁸O for oxygen, will provide a similar kinetic isotope effects.

C. FORMULATION OF PHARMACEUTICAL COMPOSITIONS

[00123] Provided herein are pharmaceutical compositions comprising a compound provided herein, *e.g.*, a compound of Formula I, as an active ingredient, or a

pharmaceutically acceptable salt, solvate or hydrate thereof; in combination with a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

[00124] The compound provided herein may be administered alone, or in combination with one or more other compounds provided herein. The pharmaceutical compositions that comprise a compound provided herein, e.g., a compound of Formula I, can be formulated in various dosage forms for oral, parenteral, and topical administration. The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Deliver Technology*, Rathbone et al., Eds., Drugs and the Pharmaceutical Science, Marcel Dekker, Inc.: New York, NY, 2003; Vol. 126).

[00125] In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise a compound provided herein, e.g., a compound of Formula I, or a pharmaceutically acceptable salt, solvate or hydrate thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00126] In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise a compound provided herein, e.g., a compound of Formula I, or a pharmaceutically acceptable salt, solvate or hydrate thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00127] In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, e.g., a compound of Formula I, or a pharmaceutically acceptable salt, solvate or hydrate thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00128] The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a

predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

[00129] In one embodiment, the therapeutically effective dose is from about 0.1 mg to about 2,000 mg per day of a compound provided herein. The pharmaceutical compositions therefore should provide a dosage of from about 0.1 mg to about 2000 mg of the compound. In certain embodiments, pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 2000 mg, from about 10 mg to about 1000 mg, from about 20 mg to about 500 mg or from about 25 mg to about 250 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form. In certain embodiments, the pharmaceutical dosage unit forms are prepared to provide about 10 mg, 20 mg, 25 mg, 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg or 2000 mg of the essential active ingredient.

Oral Administration

[00130] The pharmaceutical compositions provided herein can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum,

bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, and flavoring agents.

[00131] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrose, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[00132] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets.

[00133] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and

Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[00134] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycals, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[00135] Suitable glidants include colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Coloring agents include any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Flavoring agents include natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Sweetening agents include sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suspending and dispersing agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium

carbamethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Solvents include glycerin, sorbitol, ethyl alcohol, and syrup. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

[00136] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[00137] The pharmaceutical compositions provided herein can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00138] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00139] The pharmaceutical compositions provided herein can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00140] The pharmaceutical compositions provided herein can be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquid or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be measured conveniently for administration.

[00141] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono-

or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations can further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00142] The pharmaceutical compositions provided herein for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00143] The pharmaceutical compositions provided herein can be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00144] Coloring and flavoring agents can be used in all of the above dosage forms.

[00145] The pharmaceutical compositions provided herein can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00146] The pharmaceutical compositions provided herein can be co-formulated with other active ingredients which do not impair the desired therapeutic action, or with substances that supplement the desired action.

PARENTERAL ADMINISTRATION

[00147] The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal,

intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[00148] The pharmaceutical compositions provided herein can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

[00149] The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[00150] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[00151] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but

are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents include those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α -cyclodextrin, β -cyclodextrin, hydroxypropyl- β -cyclodextrin, sulfobutylether- β -cyclodextrin, and sulfobutylether 7- β -cyclodextrin (CAPTISOL[®], CyDex, Lenexa, KS).

[00152] The pharmaceutical compositions provided herein can be formulated for single or multiple dosage administration. The single dosage formulations are packaged in an ampoule, a vial, or a syringe. The multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00153] In one embodiment, the pharmaceutical compositions are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[00154] The pharmaceutical compositions provided herein can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00155] The pharmaceutical compositions can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[00156] Suitable inner matrixes include polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[00157] Suitable outer polymeric membranes include polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

Topical Administration

[00158] The pharmaceutical compositions provided herein can be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, includes (intra)dermal, conjunctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, urethral, respiratory, and rectal administration.

[00159] The pharmaceutical compositions provided herein can be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, dermal patches.

The topical formulation of the pharmaceutical compositions provided herein can also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

[00160] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations provided herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryoprotectants, lyoprotectants, thickening agents, and inert gases.

[00161] The pharmaceutical compositions can also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis, or microneedle or needle-free injection, such as POWDERJECT™ (Chiron Corp., Emeryville, CA), and BIOJECT™ (Bioject Medical Technologies Inc., Tualatin, OR).

[00162] The pharmaceutical compositions provided herein can be provided in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon vehicles, including lard, benzoinated lard, olive oil, cottonseed oil, and other oils, white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, including polyethylene glycols of varying molecular weight; emulsion vehicles, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid (*see, Remington: The Science and Practice of Pharmacy*, supra). These vehicles are emollient but generally require addition of antioxidants and preservatives.

[00163] Suitable cream base can be oil-in-water or water-in-oil. Cream vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the "internal" phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation may be a nonionic, anionic, cationic, or amphoteric surfactant.

[00164] Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, CARBOPOL®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

[00165] The pharmaceutical compositions provided herein can be administered rectally, urethrally, vaginally, or perivaginally in the forms of suppositories, pessaries, bougies, poultices or cataplasms, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes as described in *Remington: The Science and Practice of Pharmacy*, supra.

[00166] Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with the pharmaceutical compositions provided herein; and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, and appropriate mixtures of mono-, di- and triglycerides of fatty acids, hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, polyacrylic acid; glycerinated gelatin. Combinations of the various vehicles may be used. Rectal and vaginal suppositories may be prepared by the compressed method or molding. The typical weight of a rectal and vaginal suppository is about 2 to about 3 g.

[00167] The pharmaceutical compositions provided herein can be administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

[00168] The pharmaceutical compositions provided herein can be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical compositions can be provided in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. The pharmaceutical compositions can also be provided as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder can comprise a bioadhesive agent, including chitosan or cyclodextrin.

[00169] Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer can be formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient provided herein, a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00170] The pharmaceutical compositions provided herein can be micronized to a size suitable for delivery by inhalation, such as about 50 micrometers or less, or about 10 micrometers or less. Particles of such sizes can be prepared using a comminuting method known to those skilled in the art, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00171] Capsules, blisters and cartridges for use in an inhaler or insufflator can be formulated to contain a powder mix of the pharmaceutical compositions provided herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate. Other suitable excipients or carriers include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions provided herein for inhaled/intranasal administration

can further comprise a suitable flavor, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium.

[00172] The pharmaceutical compositions provided herein for topical administration can be formulated to be immediate release or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted, and programmed release.

Modified Release

[00173] The pharmaceutical compositions provided herein can be formulated as a modified release dosage form. As used herein, the term “modified release” refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphorism of the active ingredient(s).

[00174] Examples of modified release include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500.

1. Matrix Controlled Release Devices

[00175] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using a matrix controlled release device known to those

skilled in the art (*see*, Takada et al in “Encyclopedia of Controlled Drug Delivery,” Vol. 2, Mathiowitz Ed., Wiley, 1999).

[00176] In one embodiment, the pharmaceutical compositions provided herein in a modified release dosage form is formulated using an erodible matrix device, which is water-swellable, erodible, or soluble polymers, including synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00177] Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; and cellulosics, such as ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethylhydroxy ethylcellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT[®], Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; and other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chloride.

[00178] In further embodiments, the pharmaceutical compositions are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device included, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-

methyl methacrylate copolymers, ethylene-vinyl acetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, and ; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate,; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00179] In a matrix controlled release system, the desired release kinetics can be controlled, for example, via the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus the polymer, and other excipients or carriers in the compositions.

[00180] The pharmaceutical compositions provided herein in a modified release dosage form can be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, melt-granulation followed by compression.

2. Osmotic Controlled Release Devices

[00181] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using an osmotic controlled release device, including one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) the core which contains the active ingredient(s); and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00182] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic

agents water-swellable hydrophilic polymers, which are also referred to as “osmopolymers” and “hydrogels,” including, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00183] The other class of osmotic agents is osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00184] Osmotic agents of different dissolution rates can be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as MANGOGEM™ EZ (SPI Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

[00185] The core can also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00186] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxylated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00187] Semipermeable membrane can also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00188] The delivery port(s) on the semipermeable membrane can be formed post-coating by mechanical or laser drilling. Delivery port(s) can also be formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the

membrane over an indentation in the core. In addition, delivery ports can be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00189] The total amount of the active ingredient(s) released and the release rate can substantially be modulated via the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00190] The pharmaceutical compositions in an osmotic controlled-release dosage form can further comprise additional conventional excipients or carriers as described herein to promote performance or processing of the formulation.

[00191] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* **1995**, 35, 1-21; Verma et al., *Drug Development and Industrial Pharmacy* **2000**, 26, 695-708; Verma et al., *J. Controlled Release* **2002**, 79, 7-27).

[00192] In certain embodiments, the pharmaceutical compositions provided herein are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients or carriers. *See, U.S. Pat. No. 5,612,059 and WO 2002/17918.* The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00193] In certain embodiments, the pharmaceutical compositions provided herein are formulated as ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxylethyl cellulose, and other pharmaceutically acceptable excipients or carriers.

3. Multiparticulate Controlled Release Devices

[00194] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated as a multiparticulate controlled release device, which comprises a multiplicity of particles, granules, or pellets, ranging from about 10 µm to about 3 mm, about 50 µm to about 2.5 mm, or from about 100 µm to about 1 mm in

diameter. Such multiparticulates can be made by the processes known to those skilled in the art, including wet-and dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, and by spray-coating seed cores. See, for example, *Multiparticulate Oral Drug Delivery*; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Marcel Dekker: 1989.

[00195] Other excipients or carriers as described herein can be blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles can themselves constitute the multiparticulate device or can be coated by various film-forming materials, such as enteric polymers, water-swellable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

4. Targeted Delivery

[00196] The pharmaceutical compositions provided herein can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, U.S. Pat. Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874.

D. EVALUATION OF THE ACTIVITY OF THE COMPOUNDS

[00197] Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess biological activities that modulate the activity of JAK kinases, including wild type and mutant JAK kinases. Such assays include, for example, biochemical assays such as binding assays, see, Fabian *et al.*, *Nature Biotechnology* **2005**, 23,329-336, radioactivity incorporation assays, as well as a variety of cell based assays.

[00198] Exemplary cell based assay methodologies include measurement of STAT5A phosphorylation, for example, by ELISA or the measurement of proliferation in leukemic cell lines such as TF-1 or HEL-2, for example, by BrdU incorporation, by fluorescent staining or by a reporter assay activated by the transcription factor STAT5. Cells useful in the assays include cells with wildtype JAK such as TF-1 or mutated JAK such as the cell line HEL-2 which express a

constitutively active JAK2 carrying the V617F mutation. Suitable cells include those derived through cell culture from patient samples as well as cells derived using routine molecular biology techniques, e.g., retroviral transduction, transfection, mutagenesis, etc.

E. METHODS OF USE OF THE COMPOUNDS AND COMPOSITIONS

[00199] Also provided herein are methods of using the disclosed compounds and compositions, or pharmaceutically acceptable salts, solvates or hydrates thereof, for the treatment, prevention, or amelioration of a disease or disorder that is mediated or otherwise affected via JAK kinase, including JAK2 kinase activity or one or more symptoms of diseases or disorders that are mediated or otherwise affected via JAK kinase, including JAK2 kinase, activity. JAK kinase can be wild type and/or mutant form of JAK2 kinase. Consistent with the description above, such diseases or disorders include without limitation: myeloproliferative disorders such as polycythemia vera (PCV), essential thrombocythemia and idiopathic myelofibrosis (IMF); leukemia such as myeloid leukemia including chronic myeloid leukemia (CML), imatinib-resistant forms of CML, acute myeloid leukemia (AML), and a subtype of AML, acute megakaryoblastic leukemia (AMKL); lymphoproliferative diseases such as myeloma; cancer including head and neck cancer, prostate cancer, breast cancer, ovarian cancer, melanoma, lung cancer, brain tumor, pancreatic cancer and renal carcinoma; and inflammatory diseases or disorders related to immune dysfunction, immunodeficiency, immunomodulation, autoimmune diseases, tissue transplant rejection, graft-versus-host disease, wound healing, kidney disease, diabetic neuropathy, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, psoriasis, allergic rhinitis, inflammatory bowel disease including Crohn's disease and ulcerative colitis (UC), systemic lupus erythematosus (SLE), arthritis, osteoarthritis, rheumatoid arthritis, osteoporosis, asthma and chronic obstructive pulmonary disease (COPD) and dry eye syndrome (or keratoconjunctivitis sicca (KCS)).

[00200] In certain embodiments, provided herein are methods of using the disclosed compounds and compositions, or pharmaceutically acceptable salts, solvates or hydrates thereof, for the treatment, prevention, or amelioration of a disease or disorder selected from myeloproliferative disorders such as polycythemia vera (PCV), essential thrombocythemia and idiopathic myelofibrosis (IMF) and hypereosinophilic

syndrome (HES); leukemia such as myeloid leukemia including chronic myeloid leukemia (CML), imatinib-resistant forms of CML, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and a subtype of AML, acute megakaryoblastic leukemia (AMKL); lymphoproliferative diseases such as myeloma; cancer including head and neck cancer, prostate cancer, breast cancer, ovarian cancer, melanoma, lung cancer, brain cancer, pancreatic cancer, gastric cancer, thyroid cancer, renal carcinoma, Kaposi's sarcoma, Castleman's disease, melanoma; and inflammatory diseases or disorders related to immune dysfunction, immunodeficiency or immunomodulation, such as tissue transplant rejection, graft-versus-host disease, wound healing, kidney disease including diabetic neuropathy; autoimmune diseases such as multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, psoriasis, allergic rhinitis, atopic dermatitis, myasthenia gravis, inflammatory bowel disease including Crohn's disease and ulcerative colitis (UC), systemic lupus erythematosus (SLE), arthritis, osteoarthritis, rheumatoid arthritis, osteoporosis, asthma and chronic obstructive pulmonary disease (COPD), inflammatory diseases of the eye including conjunctivitis, uveitis, iritis, scleritis, inflammatory diseases of the respiratory tract including the upper respiratory tract such as rhinitis and sinusitis and inflammatory diseases of the lower respiratory tract including bronchitis; inflammatory myopathy such as myocarditis, other inflammatory diseases such as ischemia reperfusion injuries related to an inflammatory ischemic event such as a stroke or cardiac arrest, and other inflammatory conditions such as systemic inflammatory response syndrome (SIRS) and sepsis.

[00201] In certain embodiments, JAK-mediated diseases and disorders include restenosis, fibrosis and scleroderma. In certain embodiments, JAK-mediated diseases include viral diseases such as Epstein Barr virus (EBV), hepatitis (hepatitis B or hepatitis C), human immunodeficiency virus (HIV), Human T-lymphotropic virus type 1 (HTLV-1), varicella-zoster virus and the human papilloma virus (HPV).

F. COMBINATION THERAPY

[00202] Furthermore, it will be understood by those skilled in the art that the compounds, isomers, and pharmaceutically acceptable salts, solvates or hydrates provided herein, including pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to treat the

conditions and diseases described above. Thus, also contemplated herein is the use of compounds, isomers and pharmaceutically acceptable salts, solvates or hydrates provided herein in combination with other active pharmaceutical agents for the treatment of the disease/conditions described herein.

[00203] In one embodiment, such additional pharmaceutical agents include without limitation anti-cancer agents, including chemotherapeutic agents and anti-proliferative agents; anti-inflammatory agents and immunomodulatory agents or immunosuppressive agents.

[00204] In certain embodiments, the anti-cancer agents include anti-metabolites (*e.g.*, 5-fluoro-uracil, cytarabine, methotrexate, fludarabine and others), antimicrotubule agents (*e.g.*, vinca alkaloids such as vincristine, vinblastine; taxanes such as paclitaxel and docetaxel), alkylating agents (*e.g.*, cyclophosphamide, melphalan, carmustine, nitrosoureas such as bischloroethylnitrosurea and hydroxyurea), platinum agents (*e.g.* cisplatin, carboplatin, oxaliplatin, satraplatin and CI-973), anthracyclines (*e.g.*, doxorubicin and daunorubicin), antitumor antibiotics (*e.g.*, mitomycin, idarubicin, adriamycin and daunomycin), topoisomerase inhibitors (*e.g.*, etoposide and camptothecins), anti-angiogenesis agents (*e.g.* Sutent®, sorafenib and Bevacizumab) or any other cytotoxic agents, (*e.g.* estramustine phosphate, prednimustine), hormones or hormone agonists, antagonists, partial agonists or partial antagonists, kinase inhibitors (such as imatinib), and radiation treatment.

[00205] In certain embodiments, the anti-inflammatory agents include methotrexate, matrix metalloproteinase inhibitors, inhibitors of pro-inflammatory cytokines (*e.g.*, anti-TNF molecules, TNF soluble receptors, and IL1) non-steroidal anti-inflammatory drugs (NSAIDs) such as prostaglandin synthase inhibitors (*e.g.*, choline magnesium salicylate and salicylsalicyclic acid), COX-1 or COX-2 inhibitors, or glucocorticoid receptor agonists such as corticosteroids, methylprednisolone, prednisone, or cortisone.

[00206] The compound or composition provided herein, or pharmaceutically acceptable salts, solvates or hydrates thereof, may be administered simultaneously with, prior to, or after administration of one or more of the above agents.

[00207] Pharmaceutical compositions containing a compound provided herein or pharmaceutically acceptable salts, solvates or hydrates thereof, and one or more of the above agents are also provided.

[00208] Also provided is a combination therapy that treats or prevents the onset of the symptoms, or associated complications of cancer and related diseases and disorders comprising the administration to a subject in need thereof, of one of the compounds or compositions disclosed herein, or pharmaceutically acceptable salts, solvates or hydrates thereof, with one or more anti-cancer agents.

G. PREPARATION OF COMPOUNDS

[00209] Starting materials in the synthesis examples provided herein are either available from commercial sources or via literature procedures (e.g., March *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, (1992) 4th Ed.; Wiley Interscience, New York). All commercially available compounds were used without further purification unless otherwise indicated. Proton (¹H) nuclear magnetic resonance (NMR) spectra were typically recorded at 300 MHz on a Bruker Avance 300 NMR spectrometer unless otherwise noted. Significant peaks are tabulated and typically include: number of protons, and multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet). Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Unless otherwise noted, low resolution mass spectra (MS) were obtained as electrospray ionization (ESI) mass spectra, which were typically recorded on a Shimadzu HPLC/MS instrument using reverse-phase conditions using a mobile phase gradients of either acetonitrile/water containing 0.05% acetic acid or MeOH/water containing 0.2% formic acid. Preparative reverse phase HPLC was typically performed using a Varian HPLC system equipped with a Phenomenex phenylhexyl, a Phenomenex Luna C18, or a Varian Pursuit diphenyl reverse phase column; typical elution conditions utilized a gradient of acetonitrile/water containing 0.05% acetic acid. Silica gel chromatography was either performed manually, typically following the published procedure for flash chromatography (Still *et al.* (1978) *J. Org. Chem.* 43:2923), or on an automated system (for example, on a Biotage SP instrument) using pre-packed silica gel columns.

[00210] It is understood that in the following description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds under standard conditions.

[00211] It will also be appreciated by those skilled in the art that in the process described below the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (*e.g.*, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R (where R is alkyl, aryl or aralkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or aralkyl esters.

[00212] Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wutz, *Protective Groups in Organic Synthesis* (1991), 2nd Ed., Wiley-Interscience.

[00213] One of ordinary skill in the art could readily ascertain which choices for each substituent are possible for the reaction conditions of each Scheme. Moreover, the substituents are selected from components as indicated in the specification heretofore, and may be attached to starting materials, intermediates, and/or final products according to schemes known to those of ordinary skill in the art.

[00214] Also it will be apparent that the compounds provided herein could exist as one or more isomers, that is E/Z isomers, enantiomers and/or diastereomers.

[00215] Compounds of formula (I) may be generally prepared as depicted in the following schemes, and unless otherwise noted, the various substituents are as defined elsewhere herein.

[00216] Standard abbreviations and acronyms as defined in *J. Org. Chem.* 2007 72(1): 23A-24A are used herein. Other abbreviations and acronyms used herein are as follows:

DCM	dichloromethane
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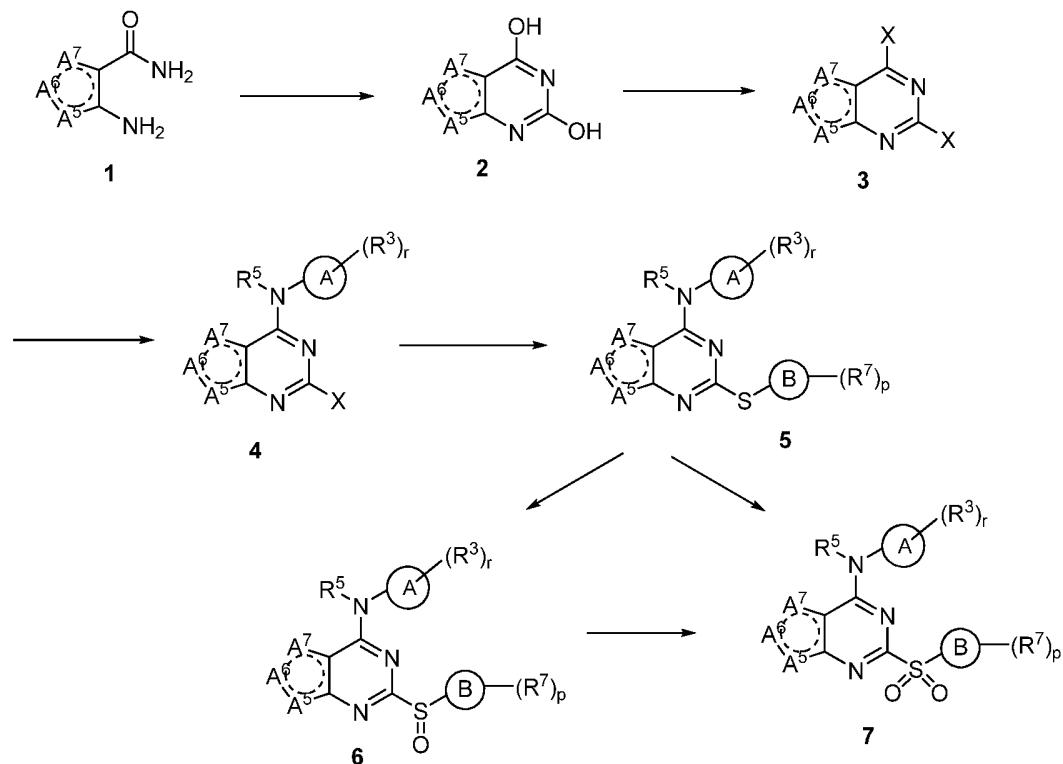
DIEA	diisopropylethylamine
EDCI	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
EtOH	ethanol
FBS	fetal bovine serum
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOAc	acetic acid
HOBT	N-hydroxybenzotriazole
MeOH	methanol
TEA	Triethylamine
Trityl	Triphenylmethyl

[00217] Compounds provided herein are synthesized according to the following schemes and descriptions.

[00218] As illustrated in Scheme 1, an appropriate aminothiophene-carboxamide **1** can be treated with phosgene or and equivalent (for example diphosgene, triphosgene, carbonyl diimidazole) to form the 2,4-dihydroxythienopyrimidine **2**, which is then treated with an appropriate phosphorous or phosphoryl halide reagent, for example phosphoryl chloride, to form the 2,4-dihalo derivative **3** (X = halo). Alternatively, X can be a different leaving group moiety, for example sulfonate, via treatment of **2** with an appropriate sulfonyl halide in the presence of base such as a tertiary amine. As a further alternative, **2** may also be transformed into **3** (X = S(O)-alkyl or S(O)₂-alkyl) by treatment with Lawesson's reagent, or P₂S₅, followed by alkylation and subsequent oxidation. When **3** is treated with an azolyl amine in the presence of tertiary amine base in a suitable solvent such as DMF or DMA with heating as necessary, preferential displacement of X at the 4-position occurs to afford **4**. Then **4** is treated with an appropriate thioalkoxide in a suitable solvent such as DMF, DMA, or an alcoholic solvent to form **5**. The sulfide of **5** is then oxidized by treatment at 0 °C to rt with a stoichiometric or slight excess quantity of an oxidant such as a percarboxylic acid to give sulfoxide **6**. Sulfone **7** is formed either from further oxidation of **6** using additional equivalents of oxidant at rt to elevated temperature as required, or

can be formed directly from **5** by treatment with two to four equivalents of oxidant at rt to elevated temperature as required to drive the reaction to substantial completion.

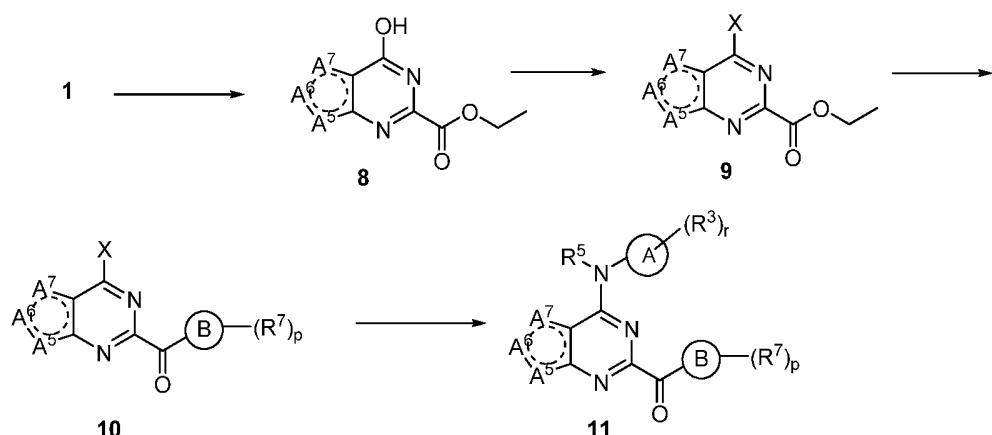
Scheme 1



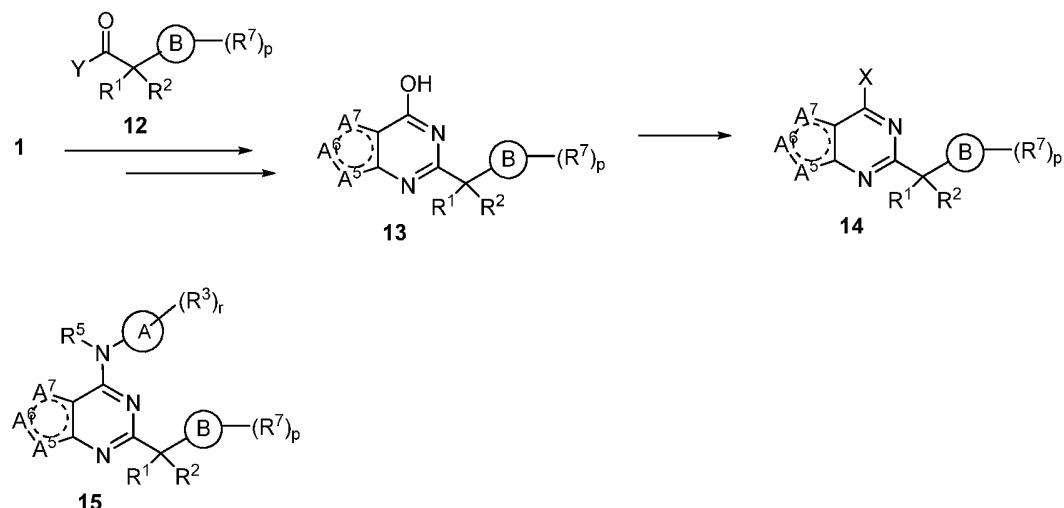
[00219] As illustrated in Scheme 2, an appropriate aminothiophene-carboxamide **1** can be transformed to a 2-carboxylate substituted thienopyrimidine **8** by treatment with an activated oxalic acid derivative such as a dialkyl oxalate either neat or in a suitable solvent such as EtOH or HOAc with heating as required. Alternatively, **1** is treated with an oxalic acid monoalkyl ester chloride in a suitable solvent such as DCM in the presence of a base such as TEA and optionally in the presence of a catalyst such as DMAP; or **1** is treated with a cyano oxoacetate monoalkyl ester with heating in a suitable solvent such as acetonitrile or DMF in the presence of a base such as TEA. Subsequent treatment under dehydrating conditions, for example, heating with or without TMSCl in the presence of a suitable base such as DIEA in a suitable solvent such as DCE affords the bicyclic product **8**. Treatment of **8** with an appropriate phosphorous or phosphoryl halide reagent, for example phosphoryl chloride, forms the 4-halo derivative **9**. Alternatively, **8** may be treated with a sulfonyl halide to form **9** (X = O-sulfonyl). As a further alternative, **8** may also be transformed into **9** (X = S(O)-alkyl or S(O)₂-alkyl) by treatment with Lawesson's

reagent, or P_2S_5 , followed by alkylation and subsequent oxidation. Treatment of **9** with a metallocarene or metalloheteroarene, for example an aryl or heteraryl lithium or an aryl or heteraryl Grignard reagent in a suitable solvent such diethyl ether, THF, or other ether solvent, produces ketone **10**. Subsequent conversion of **10** to **11** is accomplished under conditions analogous to those described in Scheme 1 for conversion of **3** to **4**.

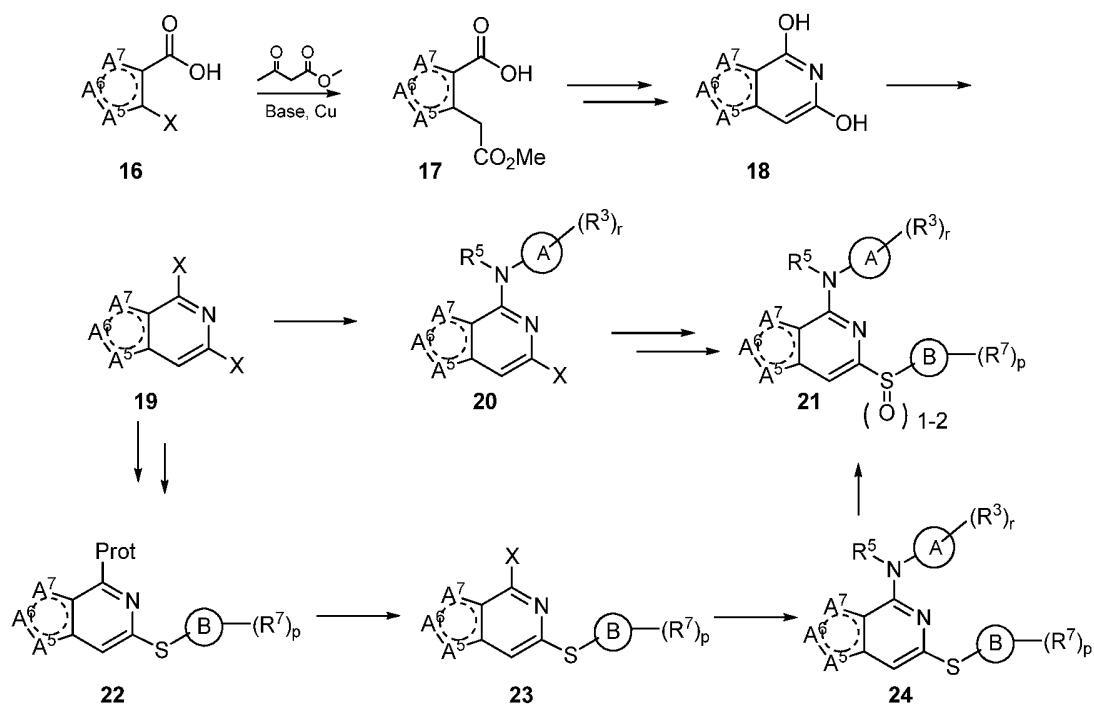
Scheme 2



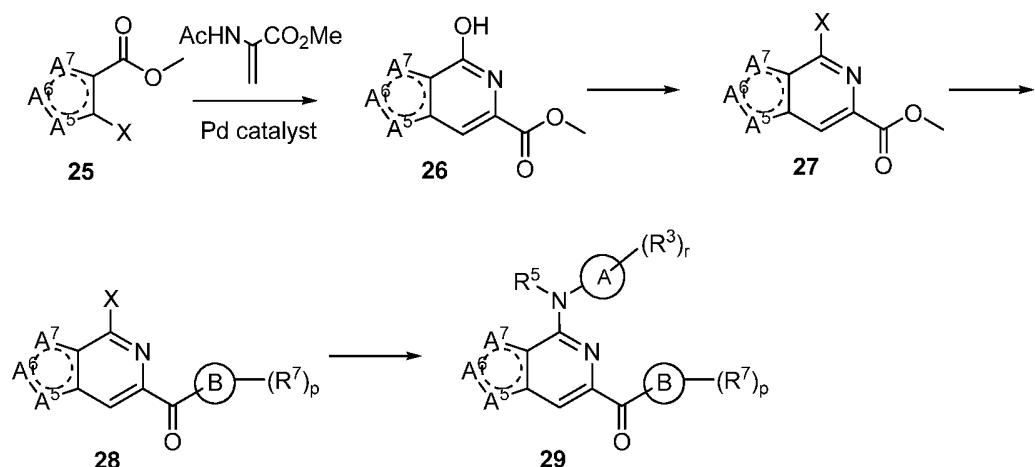
[00220] As illustrated in Scheme 3, compounds **1** may be condensed with a suitably activated carboxylic acid derivative **12** followed by dehydrative cyclization, promoted for example, with heat or with $TMSCl$ in the presence of a tertiary amine base such as TEA, DIEA, or pyridine to form 4-hydroxy derivatives **13**. Alternatively, heating of **1** with a carboxylic acid (**12**, $Y = OH$), or its salt, in the presence of trimethylsilyl polyphosphate affords **13**. Treatment of **13** with an appropriate phosphorous or phosphoryl halide reagent, for example phosphoryl chloride, forms the 4-halo derivative **14**. Alternatively, **13** may be treated with a sulfonyl halide in the presence of base to form **14** ($X = O$ -sulfonyl). As a further alternative, **13** may also be transformed into **14** ($X = S(O)$ -alkyl or $S(O)_2$ -alkyl) by treatment with Lawesson's reagent, or P_2S_5 , followed by alkylation and subsequent oxidation. Subsequent conversion of **14** to **15** is accomplished under conditions analogous to those described in Scheme 1 for conversion of **3** to **4**.

Scheme 3

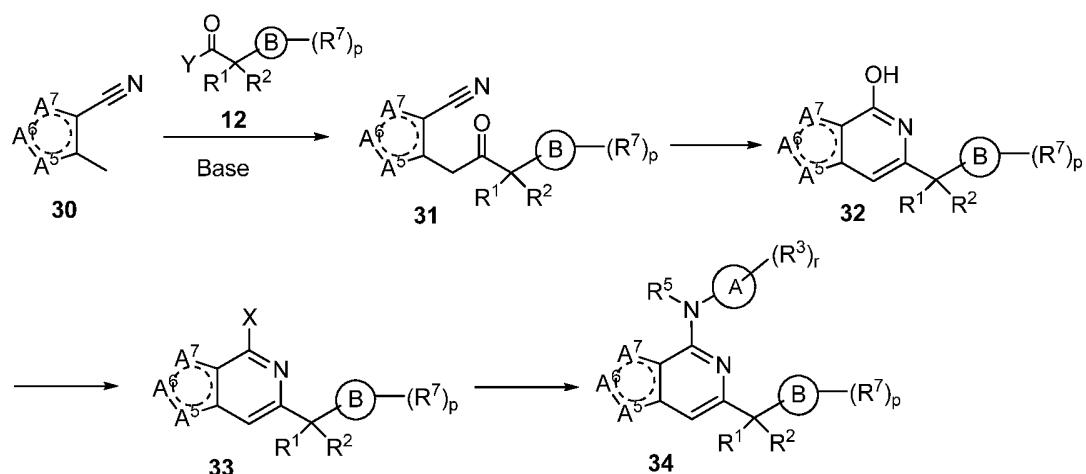
[00221] In Scheme 4 is illustrated synthetic methodology suitable for preparation of thienopyridines **21**. Treatment of an appropriate halothiophene carboxylic acid **16** with acetoacetate ester and subsequent processing under conditions described in the literature (see Bender and Sarantakis, Org Prep Proc Int 1986, 18, 286-289 and references therein), **18** is formed. The hydroxyl groups of **18** are converted to leaving groups X in a manner analogous to that described in Scheme 1 for conversion of **2** to **3** to form **19**. Treatment of **19** with an aminoazole with heating as required in the presence of acid or base or in the presence of a suitable Pd catalyst with added Pd ligands as required affords **20**. Treatment of **20** with a suitable thiolate reagent with heating as required forms an intermediate sulfide, which is oxidized to sulfoxides or sulfones **21** in a manner analogous to that described in Scheme 1 for conversion of **5** to **6** or **7**. In some cases it may be advantageous to displace one of the X groups of **19** with a group “Prot” followed by reaction with a thiolate reagent to form **22**. “Prot” is intended to be a group, for example alkoxy, which can be subsequently conveniently reverted to a leaving group X, for example to afford **23**. Conversion of **23** to **24** is effected under conditions analogous to, or if needed, more forcing than, those that used to effect conversion of **19** to **20**. Conversion of **24** to **21** is carried out under conditions analogous to those described in Scheme 1 for the conversion of **5** to **6** or **7**.

Scheme 4

[00222] In Scheme 5 is illustrated synthetic methodology suitable for preparation of thienopyridines **29**. A suitable halothiophene carboxylic ester **25** is treated with 2-acetamidoacrylate ester in the presence of a Pd catalyst, for example palladium acetate, with heating in a suitable solvent such as DMF to form **26**. The hydroxyl group of **26** is converted to a leaving group X to form **27** in a manner analogous to that described in Scheme 1 for conversion of **2** to **3**. Treatment of **27** with a metalloarene or metalloc heteroarene, for example an aryl or heteroaryl lithium or an aryl or heteroaryl Grignard reagent in a suitable solvent such diethyl ether, THF, or other ether solvent, produces ketone **28**. Treatment of **28** with an aminoazole with heating as required in the presence of acid or base or in the presence of a suitable Pd catalyst with added Pd ligands as required affords **29**.

Scheme 5

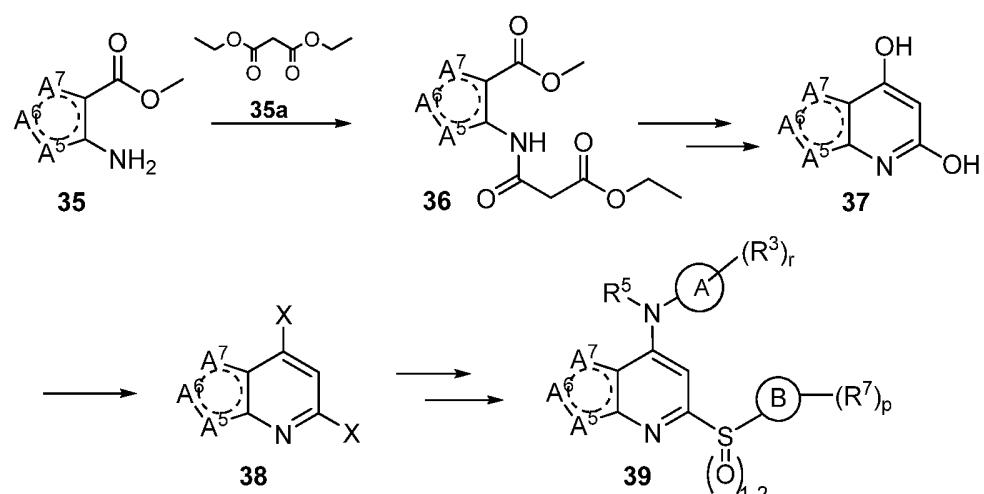
[00223] In Scheme 6 is illustrated synthetic methodology suitable for preparation of thienopyridines **34**. In a manner analogous to procedures described in WO2003/106421, a suitable methylthiophene carbonitrile **30** is deprotonated using strong base and then treated with a suitably activated carboxylic acid **12**, wherein Y may be alkoxy or $-\text{N}(\text{Me})\text{OMe}$, to form ketone **31**. Treatment of **31** under acidic conditions effects ring closure to the fused hydroxypyridine derivative **32**. The hydroxyl group of **32** is converted to a leaving group X to form **33** in a fashion analogous to that described in Scheme 1 for conversion of **2** to **3**. Treatment of **33** with an aminoazole with heating as required in the presence of acid or base or in the presence of a suitable Pd catalyst with added Pd ligands as required affords **34**.

Scheme 6

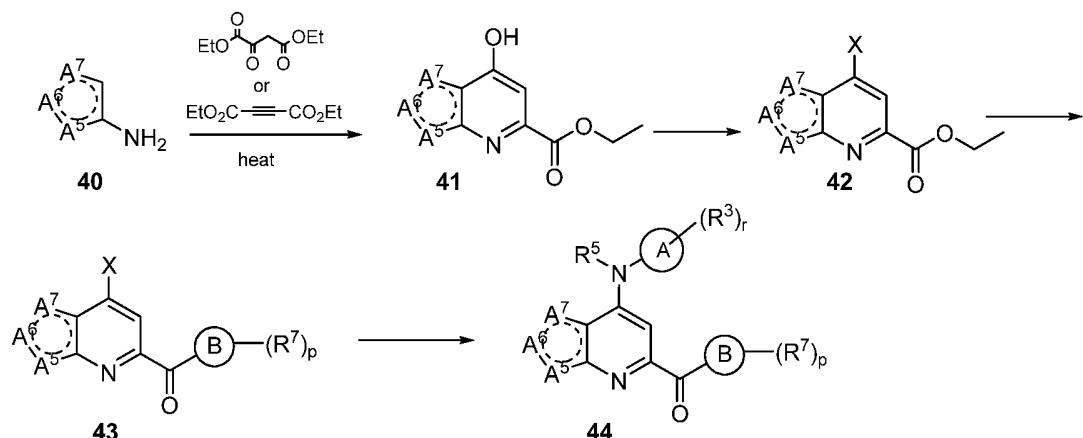
[00224] In Scheme 7 is illustrated synthetic methodology suitable for preparation of thienopyridines **39**. As described by Barker, et al. (J. Chem. Res. 1985, 5, 214-

215), treatment of a suitable aminothiophene carboxylic ester **35** with a dialkyl malonate such as **35a** affords amide **36**. Alternatively, as described in WO2006/61642, treatment of **35** with an alkyl 3-chloro-3-oxopropanoate in the presence of a tertiary amine base affords **36**. Treatment of **36** with a base such as sodium hydride or an alkoxide with heating effects ring closure, which is followed by ester hydrolysis and decarboxylation to afford **37**. Conversion of **37** to **39** via **38** is effected using methodology analogous to that described in Scheme 4 for conversion of **18** to **21**.

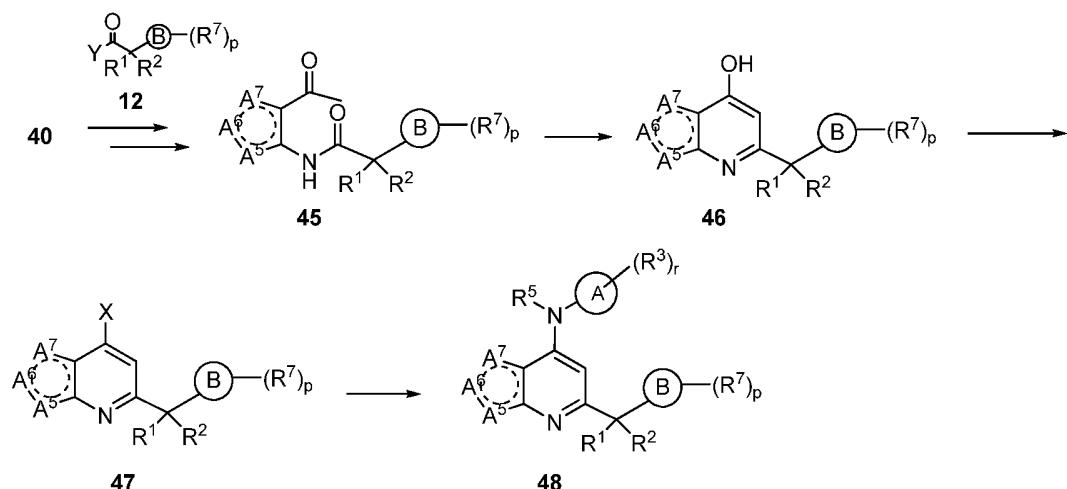
Scheme 7



[00225] In Scheme 8 is illustrated synthetic methodology suitable for preparation of thienopyridines **44**. As described in US5026700, treatment of a suitable aminothiophene **40** with dialkyl acetylenedicarboxylate in refluxing alcohol solvent affords fused hydroxypyridine **41**. Alternatively, dialkyl 2-oxosuccinate may be substituted for dialkyl acetylenedicarboxylate. Conversion of **41** to **44** via **42** and **43** may be effected using methodology analogous to that described in Scheme 5 for converting **26** to **29**.

Scheme 8

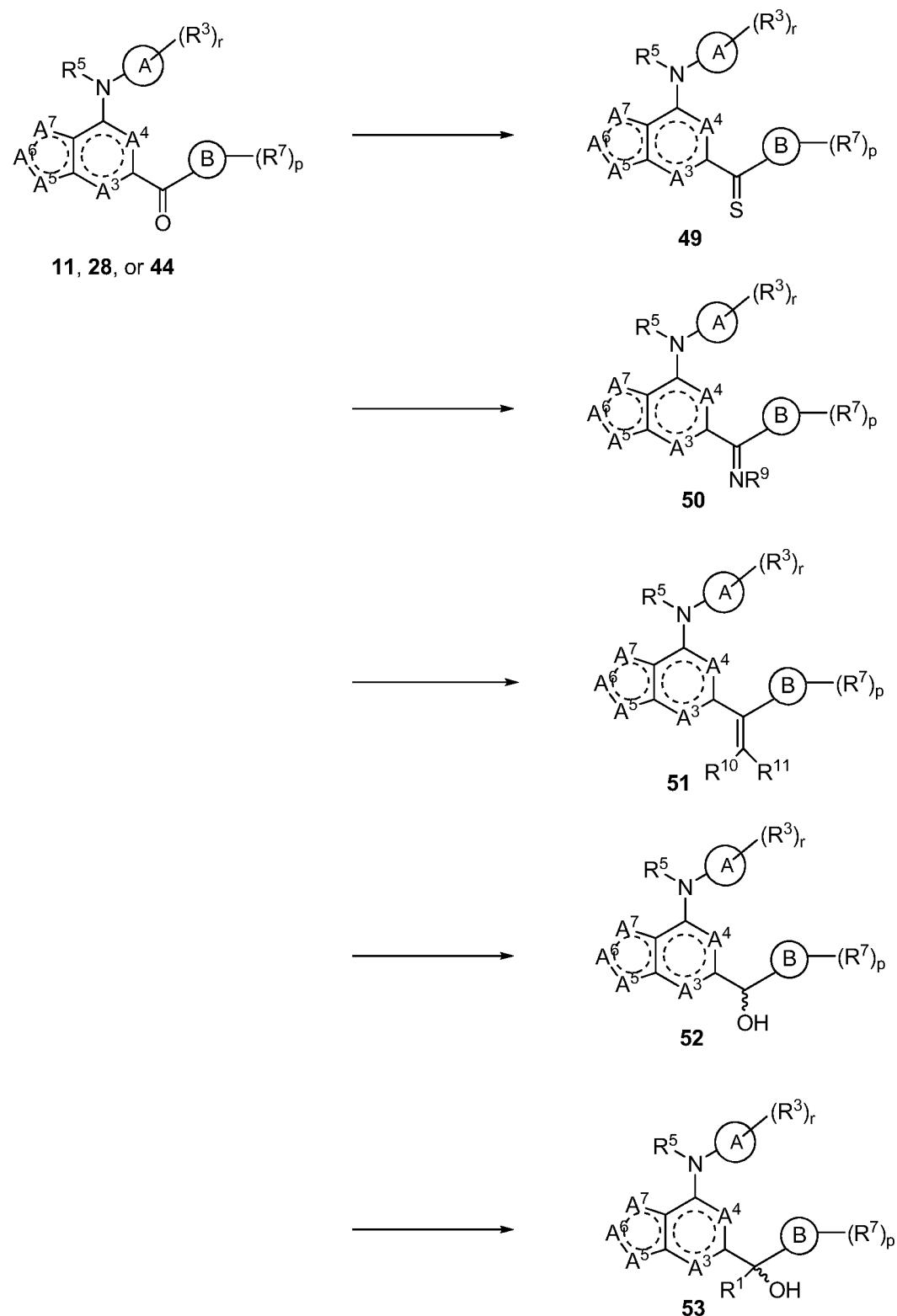
[00226] In Scheme 9 is illustrated synthetic methodology suitable for preparation of thienopyridines **48**. A suitable aminothiophene **40** is acetylated under Friedel-Crafts conditions and then the amino group is acylated with a suitably activated carboxylic acid derivative **12** to afford amide **45**. Ring closure to **46** is effected by treatment with a base such as hydroxide or alkoxide with heating as required. Conversion of **46** to **48** via **47** is effected using methodology analogous to that described in Scheme 6 for conversion of **32** to **34**.

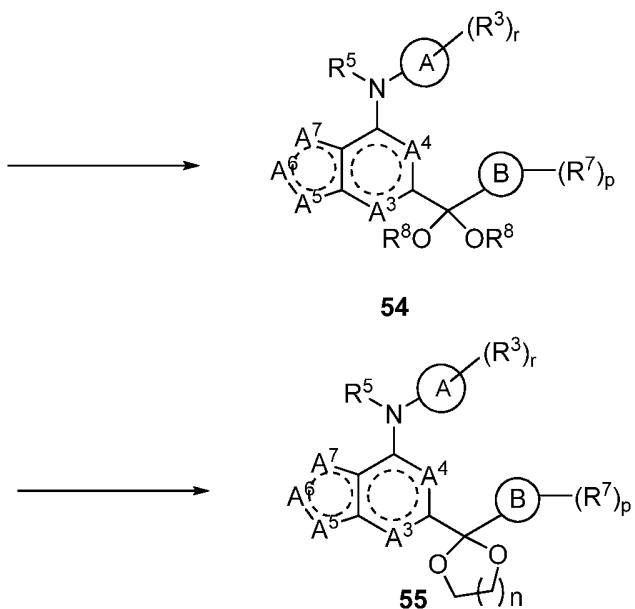
Scheme 9

[00227] In Scheme 10 are illustrated representative examples by which the keto group in any of **11** (Scheme 2), **29** (Scheme 5), or **44** (Scheme 8) can be further modified to afford additional compounds of the invention. Treatment of ketone with Lawesson's reagent affords thioketones **49**. Treatment of ketone with an amine,

hydroxylamine, or alkoxyamine under dehydrating conditions optionally in the presence of acid with heating affords, respectively, imines, oximes, or O-alkyl oximes

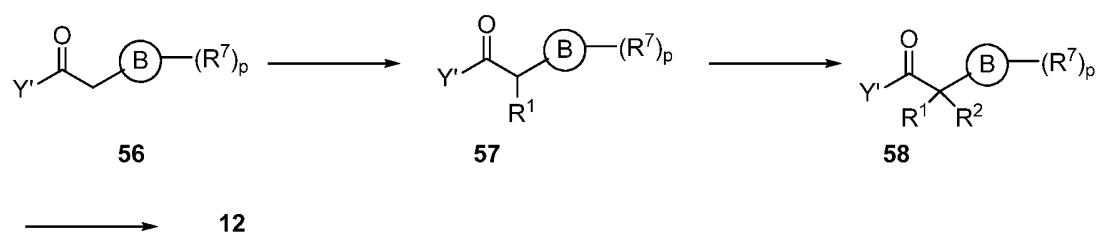
50. Treatment of ketone with a Wittig reagent or Horner-Emmons reagent affords olefins **51**. Treatment of ketone with a reducing agent such as sodium borohydride or lithium borohydride affords secondary alcohols **52**. Treatment of ketone with an organometallic reagent such as a Grignard reagent or an organolithium compound affords tertiary alcohols **53**. Heating ketone with an alcohol in the presence of acid with removal of water affords ketals **54**. Heating ketone with a 1,2- 1,3- or 1, 4 diol in the presence of acid with removal of water affords cyclic ketals **55**.

Scheme 10**Scheme 10 (continued)**



[00228] In Scheme 11 is illustrated a useful method for preparing acids **12** used in Schemes 3, 6, and 9. A carboxylic acid derivative **56**, where Y' is for example alkoxy or a subsequently removable chiral auxiliary, is deprotonated at the alpha position with a strong base and treated with an alkylating agent to afford **57**. The sequence is repeated with the same or a different alkylating agent to form **58**. The Y' group of **58** is then converted by procedures well known in the art to the Y group of **12** that is suitable for use in Scheme 3, 6, or 9.

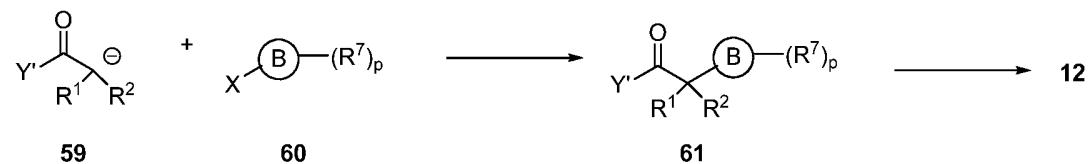
Scheme 11



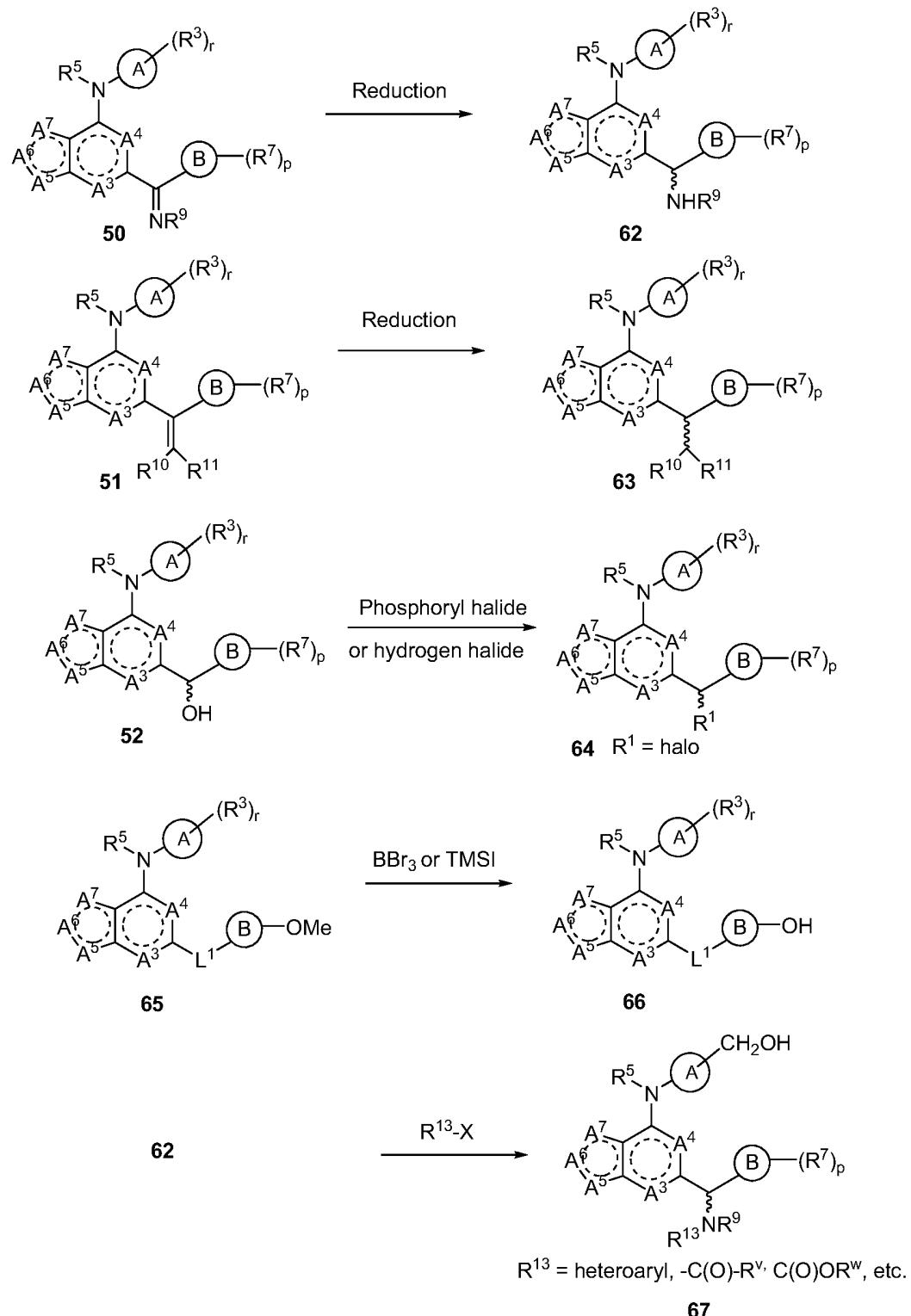
[00229] In Scheme 12 is illustrated an alternative method for preparing acids **12** used in Schemes 3, 6, and 9. A suitable carboxylic acid derivative, following conversion with base to an enolate **59** or its equivalent is treated with an aryl halide, or more suitably with a heteroaryl halide to form **61**. The Y' group of **61** is then

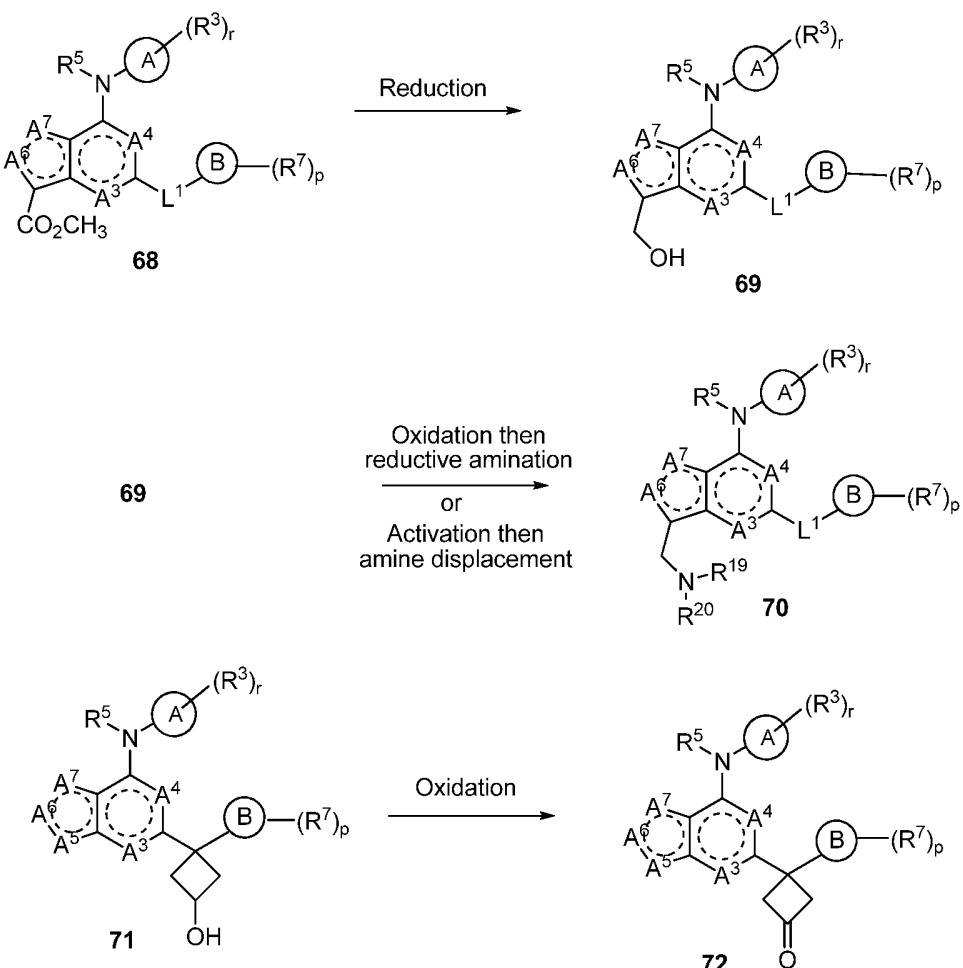
converted by procedures well known in the art to the Y group of **12** that is suitable for use in Scheme 3, 6, or 9.

Scheme 12



[00230] It will be appreciated by one skilled in the art that standard functional group manipulations may be used to prepare additional compounds of the invention from products or intermediates prepared as described by the foregoing methods. In Scheme 13 are shown representative examples that are intended to illustrate, but in no way to limit the scope of, such standard functional group manipulations.

Scheme 13**Scheme 13 (continued)**

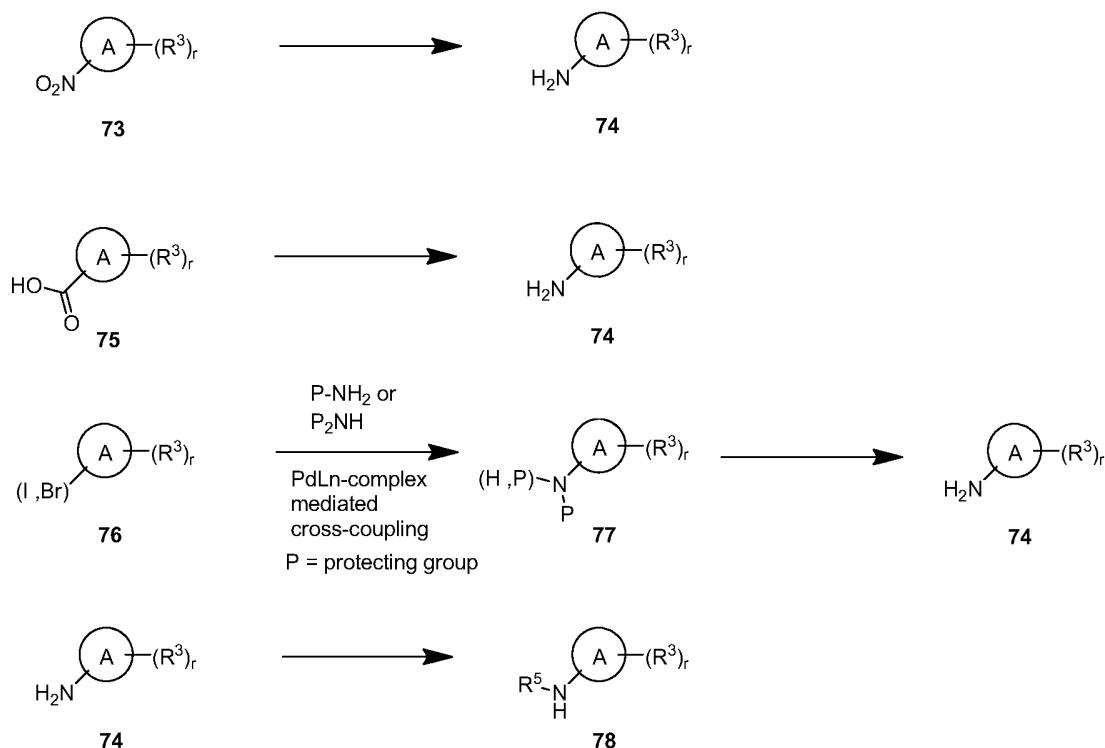


[00231] Aminoazole or azolyl amine intermediates employed herein may be obtained either via commercial sources or prepared using methods known to those skilled in the art. Scheme 14 illustrates representative methods that may be employed for the preparation of additional aminoazoles or azolyl amines. For example, nitroazoles **73** may be converted to aminoazoles **74** via treatment with a suitable reducing agent such as SnCl_2 in a suitable solvent such as DCE or EtOH optionally in the presence of HCl, with heating. Alternatively, treatment of **73** with activated iron or zinc metal in HOAc with heating, will afford **74**. Alternatively, treatment of **73** with palladium metal on activated carbon in the presence of ≥ 1 atmosphere pressure of hydrogen gas, in a suitable solvent such as MeOH, EtOH, or EtOAc or mixtures of these, at rt or with heating as required, will afford **74**. Alternatively treatment of **73** with sodium hydrosulfite in a suitable solvent mixture such as THF and water at rt or with heating as required, will afford **74**. Alternatively, aminoazoles **74** may also be obtained from azole carboxylic acids **75** via initial treatment with diphenylphosphoryl

azide in the presence of an organic base such as TEA, and in a suitable solvent such as toluene or THF, and with heating from 50 °C to 150 °C as required, followed by hydrolysis. Alternatively, treatment of **75** with diphenylphosphoryl azide in the presence of an organic base such as TEA, and in the presence of excess *tert*-butanol, and in a suitable solvent such as toluene or THF, and with heating from 50 °C to 150 °C as required, will afford a *tert*-butylcarbamoyl azole intermediate, which upon treatment with an acid such as TFA or HCl in a suitable solvent, will afford **74**. Aminoazoles **74** may also be obtained from azolyl bromides or iodides **76**, bearing (as required) suitable protecting groups on any azole ring N-H positions, via initial treatment with a suitable amino containing reagent (where P = protecting group), such as benzophenone imine, 2,4-dimethoxybenzylamine, or *tert*-butyl carbamate, and in the presence of a catalytic amount of a suitable organopalladium-complex, and optionally in the presence of a suitable phosphine-ligand, and optionally in the presence of a suitable base, and in a suitable solvent at elevated temperature or under microwave conditions, to afford intermediate **77**. Subsequent N-deprotection of intermediate **77** (including azole ring N-deprotection, where required), employing appropriate methods known to those skilled in the art will afford **74**. Conversion of aminoazoles **74** to alkylated aminoazoles **78** may be achieved via treatment of **74** with an appropriate aldehyde or ketone substrate, in the presence of a suitable Lewis acid such as TMSCl or TiCl₄ and a reducing agent such as sodium (triacetoxy)borohydride or sodium cyanoborohydride, in a suitable organic solvent such as DCM, DCE, THF, or MeOH, optionally in the presence of HOAc, at rt or with heating as required. Alternatively, **78** may be obtained via treatment of **74** with an alkyl halide in the presence of a suitable organic base such as pyridine or DIEA, and sodium or potassium iodide, and in a suitable solvent such as DMF or THF, at rt or with heating as required. Nitroazoles **73**, azole carboxylic acids **75**, and azole bromides or iodides **76** may be obtained from commercial sources or prepared using methods known to those skilled in the art.

Scheme 14

[00232]



[00233] The subject matter has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation. Thus, it will be appreciated by those of skill in the art that conditions such as choice of solvent, temperature of reaction, volumes, reaction time may vary while still producing the desired compounds. In addition, one of skill in the art will also appreciate that many of the reagents provided in the following examples may be substituted with other suitable reagents. *See, e.g., Smith & March, Advanced Organic Chemistry, 5th ed. (2001).* Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and/or methods of use provided herein, may be made without departing from the spirit and scope thereof. U.S. patents and publications referenced herein are incorporated by reference.

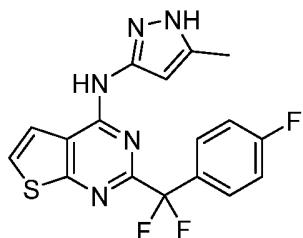
EXAMPLES

[00234] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials,

and procedures. All such equivalents are considered to be within the scope of the claimed subject matter and are encompassed by the appended claims.

Example 1

Preparation 2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine



[00235] **Step A:** To a stirred solution of 2,2-difluoro-2-(4-fluorophenyl)acetic acid (1.61 g, 8.47 mmol) in DMF (15 mL) at rt were added HATU (3.23 g, 8.49 mmol) and DIEA (1.74 mL, 10.0 mmol) and the mixture was stirred at rt for 10 min. 2-Aminothiophene-3-carboxamide (1.1 g, 7.74 mmol) was added and the mixture was stirred at rt for 15 h, then water (50 mL) was added dropwise, whereupon a dark oil separated. The supernatant was decanted, and the residual oil was partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 2-(2,2-difluoro-2-(4-fluorophenyl)acetamido)thiophene-3-carboxamide (2.30 g, 95%). LC-MS (ESI) m/z 315 ($M + H$)⁺.

[00236] **Step B:** A stirred mixture of 2-(2,2-difluoro-2-(4-fluorophenyl)acetamido)thiophene-3-carboxamide (2.30g, 7.32 mmol), trimethylsilyl chloride (13.8 mL, 109 mmol), and TEA (38.9 mL, 280 mmol) in DCE (40 mL) was heated at 85 °C for 18 h. The reaction mixture was subjected to aqueous work up to afford 2-(difluoro(4-fluorophenyl)methyl)thieno[2,3-d]pyrimidin-4-ol (1.8 g, 83%).

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 7.36 – 7.46 (m, 3H), 7.64 – 7.75 (m, 3H), 13.40 (brs, 1H); LC-MS (ESI) m/z 297 ($M + H$)⁺.

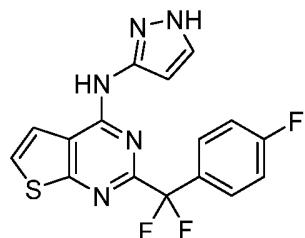
[00237] **Step C:** 4-Chloro-2-(difluoro(4-fluorophenyl)methyl)thieno[2,3-d]pyrimidine was prepared using a procedure similar to that described in Example 3 Step D, substituting 2-(difluoro(4-fluorophenyl)methyl)thieno[2,3-d]pyrimidin-4-ol

for the ethyl 4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxylate used in Example 3.

[00238] **Step D:** A stirred mixture of 4-chloro-2-(difluoro(4-fluorophenyl)methyl)thieno[2,3-d]pyrimidine (200 mg, 0.63 mmol), 5-methyl-1H-pyrazol-3-amine (68 mg, 0.70 mmol), potassium iodide (105 mg, 0.63 mmol), and DIEA (131 mg, 0.76 mmol) in DMF (3 mL) was heated at 50 °C for 5 h. The mixture was subjected to an aqueous work up and the crude product was purified by preparative reverse phase HPLC to afford 2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine as a solid (27 mg, 11%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 2.21 (s, 3H), 6.22 (s, 1H), 7.33 – 7.39 (m, 2H), 7.67 – 7.71 (m, 2H), 7.79 (m, 1H), 7.99 (m, 1H), 10.64 (brs, 1H), 12.16 (brs, 1H); LC-MS (ESI) *m/z* 376 (M + H)⁺.

Example 2

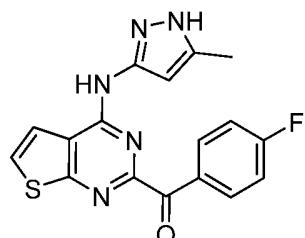
Preparation 2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine



[00239] A stirred mixture of 4-chloro-2-(difluoro(4-fluorophenyl)methyl)thieno[2,3-d]pyrimidine from Example 1 Step C (200 mg, 0.63 mmol), 1H-pyrazol-3-amine (58 mg, 0.70 mmol), potassium iodide (105 mg, 0.63 mmol) and DIEA (131 mg, 0.76 mmol) in DMF (3 mL), was heated at 50 °C for 5 h. The mixture was submitted to an aqueous work up and the crude product was purified by preparative reverse phase HPLC to afford 2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine as a solid (11 mg, 5%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 6.70 (s, 1H), 7.30 – 7.36 (m, 2H), 7.66 – 7.71 (m, 3H), 7.80 (m, 1H), 8.01 (m, 1H), 10.78 (brs, 1H), 12.51 (brs, 1H); LC-MS (ESI) *m/z* 362 (M + H)⁺.

Example 3

Preparation (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanone



[00240] **Step A:** A stirred mixture of 2-cyanoacetamide (2 g, 23.8 mmol), 1,4-dithiane-2,5-diol (3.6 g, 23.8 mmol) and TEA (4.8 g, 47.6 mmol) in EtOH was heated at reflux for 5 h. After cooling to rt, the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc (200 mL) and 1 M aq sodium hydroxide (300 mL). The organic layer was separated and washed with water and brine., dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 2-aminothiophene-3-carboxamide (2.78 g, 82%). ^1H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.23 (d, *J* = 6 Hz, 1H), 6.76 (brs, 2H), 7.05 (d, *J* = 6 Hz, 1H), 7.23 (brs, 2H); LC-MS (ESI) *m/z* 143 (M + H)⁺.

[00241] **Step B:** To a stirred solution of 2-aminothiophene-3-carboxamide (200 mg, 1.41 mmol) and TEA (170 mg, 1.68 mmol) in DCM (7 mL) at 0 °C was added ethyl chlorooxoacetate (230 mg, 1.68 mmol). The mixture was allowed to warm to rt and stir for a further 5 h. The mixture was partitioned between EtOAc and water, and the separated organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford ethyl 2-(3-carbamoylthiophen-2-ylamino)-2-oxoacetate (200 mg). LC-MS (ESI) *m/z* 243 (M + H)⁺.

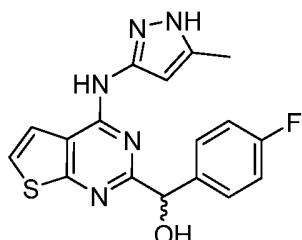
[00242] **Step C:** To a stirred suspension of ethyl 2-(3-carbamoylthiophen-2-ylamino)-2-oxoacetate (300 mg, 1.24 mmol) in DCM (10 mL) were added TEA (0.8 mL, 6.20 mmol) and trimethylsilyl chloride (0.5 mL, 3.72 mmol). The mixture was heated at reflux for 5 h, then EtOAc was added and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with DCM/MeOH to afford ethyl 4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxylate as a brown solid (100 mg, 36%). ^1H

NMR (400 MHz, DMSO-*d*₆) δ ppm 1.35 (t, *J* = 7.2 Hz, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 7.51 (d, *J* = 5.6 Hz, 1H), 7.81 (d, *J* = 5.6 Hz, 1H); LC-MS (ESI) *m/z* 225 (M + H)⁺.

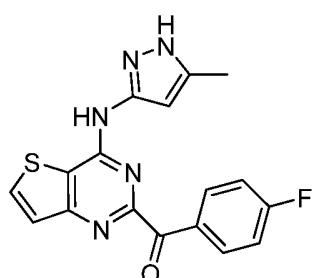
[00243] **Step D:** A stirred mixture of ethyl 4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxylate (112 mg, 0.50 mmol) and phosphorus oxychloride (3 mL) was heated at reflux for 3 h. The mixture was concentrated under reduced pressure and the residue was partitioned between ice water and EtOAc. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford ethyl 4-chlorothieno[2,3-d]pyrimidine-2-carboxylate (85 mg). LC-MS (ESI) *m/z* 243 (M + H)⁺.

[00244] **Step E:** To a stirred mixture of ethyl 4-chlorothieno[2,3-d]pyrimidine-2-carboxylate (85 mg, 0.35 mmol) in THF (2 mL) at -30 °C, was added 1M 4-fluorophenylmagnesium bromide/Et₂O (0.021 mL, 0.42 mmol) and the mixture was stirred at -30 °C for 30 min. To the mixture was added 1 M HCl and the mixture was extracted with EtOAc. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford (4-chlorothieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (62 mg). LC-MS (ESI) *m/z* 293 (M + H)⁺.

[00245] **Step F:** To a stirred mixture of (4-chlorothieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (65 mg, 0.22 mmol) in DMF (1 mL) were added 5-methyl-1H-pyrazol-3-amine (43 mg, 0.44 mmol) and 4M HCl/1,4-dioxane (0.025 mL, 0.10 mmol) and the mixture was heated at 90 °C for 1 h. The mixture was poured into water and the resulting precipitate was collected by filtration and dried. The solid was purified by reverse phase preparative HPLC to afford (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanone as a solid (45 mg, 58%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.17 (s, 3H), 6.47 (s, 1H), 7.38 – 7.43 (m, 2H), 7.86 (d, *J* = 6 Hz, 1H), 8.07 – 8.11 (m, 3H), 10.63 (brs, 1H), 12.18 (brs, 1H); LC-MS (ESI) *m/z* 354 (M + H)⁺.

Example 4**Preparation (*R,S*)-(4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanol**

[00246] To a stirred mixture of (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanone from Example 3 (800 mg, 2.27 mmol) in MeOH (50 mL) at 0 °C was added sodium borohydride (172 mg, 4.53 mmol). The mixture was allowed to warm to rt and stir for 1 h. The mixture was concentrated under reduced pressure and the residue was poured into water. The resulting solid was collected by filtration and washed with water and then brine. The solid was purified by recrystallization from a mixture of EtOAc and MeOH to afford (*R,S*)-(4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanol as a yellow solid (560 mg, 69%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.24 (s, 3H), 5.70 (s, 1H), 5.90 (brs, 1H), 6.44 (brs, 1H), 7.12 – 7.17 (m, 2H), 7.51 – 7.61 (m, 3H), 7.89 (brs, 1H), 10.32 (brs, 1H), 12.09 (brs, 1H); LC-MS (ESI) *m/z* 356 (M + H)⁺.

Example 5**Preparation of (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanone**

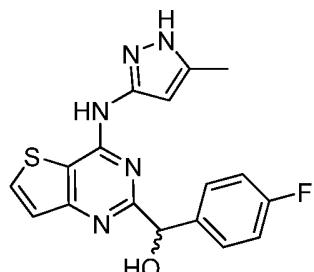
[00247] **Step A:** To a solution of methyl 3-aminothiophene-2-carboxylate (3.0 g, 0.019 mol) in acetic acid (24 mL) were added concentrated hydrochloric acid (2.4 mL) and ethyl cyanoformate (3.78 g, 0.038 mol). The heterogeneous mixture was

heated at 70 °C for 3 h, and then allowed to cool to rt. The solid was collected by filtration and washed with water. The pH of the filtrate was adjusted to about 5 by addition of 1N NaOH, and the precipitated solid was collected by filtration and washed with water. The solids were combined and left under vacuum overnight to afford ethyl 4-oxo-3,4-dihydrothieno[3,2-d]pyrimidine-2-carboxylate (2.69 g, 63%).

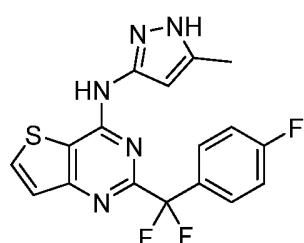
[00248] **Step B:** A mixture of ethyl 4-oxo-3,4-dihydrothieno[3,2-d]pyrimidine-2-carboxylate (2.6 g, 11.6 mmol) in phosphorus oxychloride (20 mL) was heated at 105 °C overnight. The mixture was concentrated under reduced pressure, and then toluene was added and evaporated under reduced pressure. The mixture was dissolved in DCM and passed through a pad of silica gel to afford ethyl 4-chlorothieno[3,2-d]pyrimidine-2-carboxylate (2.25 g, 80%). LC-MS (ESI) *m/z* 243 (M + H)⁺.

[00249] **Step C:** To a solution of 4-chlorothieno[3,2-d]pyrimidine-2-carboxylate (2.25 g, 9.29 mmol) in THF (120 mL) at -40 °C was added 1 M 4-fluorophenylmagnesium bromide (12 mL, 12 mmol) and the mixture was stirred at -40 to -30 °C for 8 h. The reaction mixture was further treated using a procedure analogous to that described in Example 3 Step D, except the crude product after aqueous workup was taken to the next step without further purification. (4-Chlorothieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone was obtained as an off-white solid (1.72 g, 63%). LC-MS (ESI) *m/z* 293 (M + H)⁺.

[00250] **Step D:** A mixture of (4-chlorothieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (1.70 g, 5.82 mmol), 5-methyl-1H-pyrazol-3-amine (1.13 g, 11.6 mmol), DIEA (1.41 mL, 8.15 mmol), and KI (0.966 g, 5.82 mmol) in DMF (20 mL) was heated at 70 °C overnight. The mixture was diluted with water and the precipitated solid was collected by filtration and washed with water. The crude solid was triturated with hot methanol to yield (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino) thieno[3,2-d]pyrimidin-2-yl)methanone as a light yellow solid (1.5 g, 73%).
¹H NMR (DMSO-*d*₆): δ 12.27 (s, 1H), 10.44 (s, 1H), 8.27 (d, 1H), 8.06 (m, 2H), 7.51 (d, 1H), 7.38 (t, 2H), 6.32 (s, 1H), 2.20 (s, 3H); LC-MS (ESI) *m/z* 354 (M + H)⁺.

Example 6**Preparation of (R,S)-4-Fluorophenyl(4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanol**

[00251] To (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl) methanone from Example 5 (1.5 g, 4.25 mmol) in 4:1 MeOH/THF (20 mL) was added sodium borohydride (0.257 g, 6.69 mmol). The mixture was stirred for 2 h and then concentrated under a stream of air. The residue was diluted with water, and the precipitated solid was collected by filtration and washed with water and diethyl ether to afford (R,S)-4-fluorophenyl(4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanol as a white solid (1.32 g, 87%). ¹H NMR (DMSO-*d*₆): δ12.16 (s, 1H), 10.30 (s, 1H), 8.14 (d, 1H), 7.52 (m, 2H), 7.40 (d, 1H), 7.13 (t, 2H), 6.29 (s, 1H), 5.79 (s, 1H), 5.68 (d, 1H), 2.24 (s, 3H); LC-MS (ESI) *m/z* 356 (M + H)⁺.

Example 7**Preparation 2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine**

[00252] **Step A:** To a stirred solution of 2,2-difluoro-2-(4-fluorophenyl)acetic acid from Example 8 Step A (190 mg, 1.0 mmol) and pyridine (0.16 mL, 2.0 mmol) in DMF (1.5 mL) at 0 °C was added dropwise pentafluorophenyl-trifluoroacetate (0.26 mL, 1.5 mmol) and the mixture was stirred for 30 min. To the mixture was added 3-aminothiophene-2-carboxamide (142 mg, 1.0 mmol) and the mixture stirred at rt for 2.5 h, then heated at 90 °C for 3 h. The mixture was added to ice water and extracted

with EtOAc. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with a mixture of DCM in MeOH to afford 3-(2,2-difluoro-2-(4-fluorophenyl)acetamido)thiophene-2-carboxamide as a brown solid (270 mg, 86%).

[00253] **Step B:** A stirred mixture of 3-(2,2-difluoro-2-(4-fluorophenyl)acetamido)thiophene-2-carboxamide (377 mg, 1.2 mmol) and HOAc (10 mL) was heated at reflux for 15 h. The mixture was concentrated under reduced pressure and the residue was dissolved in HOAc (10 mL). The resulting mixture was added acetic anhydride (2 mL, 21.2 mmol) and the mixture was heated at reflux for 15 h. The mixture was concentrated under reduced pressure and the residue was triturated with EtOAc. The solid was collected by filtration washing with petroleum ether to afford 2-(difluoro(4-fluorophenyl)methyl)thieno[3,2-d]pyrimidin-4-ol as a brown solid (300 mg, 85%). ^1H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.37 – 7.42 (m, 2H), 7.49 (d, *J* = 5.2 Hz, 1H), 7.73 – 7.77 (m, 2H), 8.28 (d, *J* = 5.2 Hz, 1H), 13.41 (br s, 1H); LC-MS (ESI) *m/z* 297 (M + H)⁺.

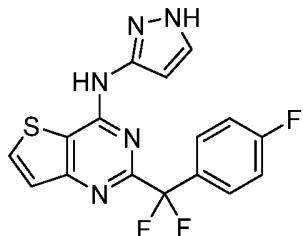
[00254] **Step C:** A stirred mixture of 2-(difluoro(4-fluorophenyl)methyl)thieno[3,2-d]pyrimidin-4-ol (296 mg, 1.0 mmol) and phosphorus oxychloride (5 mL) was heated at reflux for 1 h. The mixture was concentrated under reduced pressure and the residue was poured into water. The mixture was basified with saturated aq sodium hydrogen carbonate and extracted with EtOAc. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 4-chloro-2-(difluoro(4-fluorophenyl)methyl)thieno[3,2-d]pyrimidine (274 mg). LC-MS (ESI) *m/z* 315 (M + H)⁺.

[00255] **Step D:** A stirred mixture of 4-chloro-2-(difluoro(4-fluorophenyl)methyl)thieno[3,2-d]pyrimidine (105 mg, 0.30 mmol), 5-methyl-1*H*-pyrazol-3-amine (97 mg, 1.0 mmol) and 4M HCl/1,4-dioxane (0.080 mL, 0.32 mmol) in DMF (1 mL) was heated at 90 °C for 3 h. The mixture was poured into water and the resulting solid precipitate was collected by filtration washing with H₂O. The solid was purified by preparative reverse phase HPLC to afford 2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1*H*-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine as a solid (35 mg, 28%). ^1H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.24 (s, 3H), 6.17 (s,

1H), 7.34 – 7.38 (m, 2H), 7.52 (d, J = 4.8 Hz, 1H), 7.68 – 7.71 (m, 2H), 8.26 (d, J = 4.8 Hz, 1H), 10.55 (br s, 1H), 12.25 (br s, 1H); LC-MS (ESI) m/z 376 ($M + H$)⁺.

Example 8

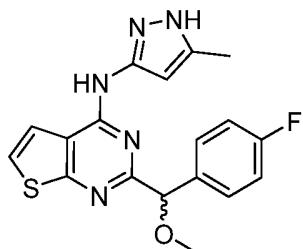
Preparation 2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine



[00256] 2-(Difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine was prepared as a colorless solid (60 mg, 50%) using a procedure analogous to that described in Example 7 Step D, substituting 3-aminopyrazole for the 5-methyl-1H-pyrazol-3-amine used in Example 7. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.61 (s, 1H), 7.31 – 7.35 (m, 2H), 7.52 (d, J = 4.4 Hz, 1H), 7.70 – 7.72 (m, 3H), 8.27 (d, J = 4.4 Hz, 1H), 10.65 (br s, 1H), 12.59 (br s, 1H); LC-MS (ESI) m/z 362 ($M + H$)⁺.

Example 9

Preparation (R, S)-2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine

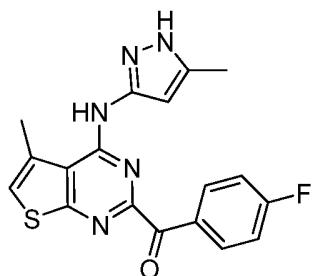


[00257] To a stirred mixture of (*R, S*)-(4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanol from Example 4 (300 mg, 0.88 mmol) in DCM (10 mL) was added phosphorus tribromide (169 μL, 1.75 mmol) and the mixture heated at 60 °C for 1 h. MeOH (30 mL) was added and the mixture was heated at 60 °C for 15 h, and then concentrated under reduced pressure. The residue was partitioned between 1:1 EtOAc/THF and water, and the organic layer was

separated and washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative reverse phase HPLC to afford (*R,S*)-2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1*H*-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine as a solid (5 mg, 2%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 2.26 (s, 3H), 3.35 (s, 3H), 5.37 (s, 1H), 6.54 (s, 1H), 7.13 – 7.19 (m, 2H), 7.50 – 7.56 (m, 2H), 7.61 (d, *J* = 6 Hz, 1H), 7.89 (d, *J* = 6 Hz, 1H), 10.34 (brs, 1H), 12.20 (brs, 1H); LC-MS (ESI) *m/z* 370 (M + H)⁺.

Example 10

Preparation of (4-fluorophenyl)(5-methyl-4-(5-methyl-1*H*-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanone



[00258] **Step A:** To a solution of ethyl 2-amino-4-methylthiophene-3-carboxylate (800 mg, 4.32 mmol) in acetic acid (4 mL) were added concentrated hydrochloric acid (0.4 mL) and ethyl cyanoformate (0.513 mL, 5.18 mmol). The heterogeneous mixture was heated at 70 °C for 4 h. After cooling to room temperature, saturated aq sodium bicarbonate was added to give pH 5. The solid was collected by filtration, washed with water, and left under vacuum overnight to afford ethyl 5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxylate as an off white solid (420 mg, 40%). ¹H NMR (DMSO-*d*₆): δ 12.72 (s, 1H), 7.39 (s, 1H), 4.36 (q, 2H), 2.50 (s, 3H), 1.34 (t, 3H); LC-MS (ESI) *m/z* 239 (M + H)⁺.

[00259] **Step B:** Ethyl 4-chloro-5-methylthieno[2,3-d]pyrimidine -2-carboxylate was prepared as a light yellow solid (350 mg, 77%) using 15 mL of phosphorus oxychloride in a procedure analogous to that described in Example 3 Step D, substituting ethyl 5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxylate (420 mg, 1.76 mmol) for the ethyl 4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxylate used in Example 3. LC-MS (ESI) *m/z* 257 (M + H)⁺.

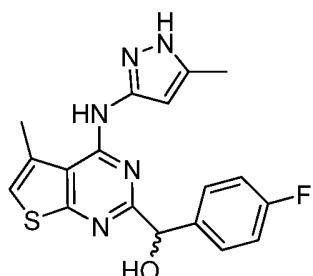
[00260] **Step C:** (4-Chloro-5-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone was prepared as an off-white solid (410 g, 81%) using a

procedure analogous to that described in Example 3 Step E, substituting ethyl 4-chloro-5-methylthieno[2,3-d]pyrimidine-2-carboxylate (350 mg, 1.36 mmol) for the ethyl 4-chlorothieno[2,3-d]pyrimidine-2-carboxylate used in Example 3. ¹H NMR (DMSO- *d*₆): δ 8.11 (t, 2H), 7.99 (s, 1H), 7.42 (t, 2H), 2.69 (s, 3H).

[00261] **Step D:** A mixture of (4-chloro-5-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (200 mg, 0.65 mmol), 5-methyl-1H-pyrazol-3-amine (127 mg, 1.3 mmol), DIEA (0.16 mL, 0.91 mmol), and KI (108 mg, 0.65 mmol) was heated at 80 °C for 18 h. The mixture was diluted with water and the precipitated solid was filtered, washed with water, and triturated with hot methanol to yield (4-fluorophenyl)(5-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanone as a light yellow solid (210 mg, 94 %). ¹H NMR (DMSO- *d*₆): δ 12.18 (s, 1H), 8.61 (s, 1H), 8.08 (t, 2H), 7.50 (s, 1H), 7.38 (t, 2H), 6.37 (s, 1H), 2.75 (s, 3H), 2.16 (s, 3H); LC-MS (ESI) *m/z* 368 (M + H)⁺.

Example 11

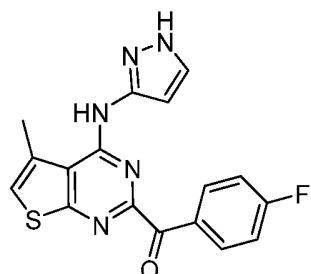
Preparation of (R,S)-(4-Fluorophenyl)(5-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanol



[00262] To (4-fluorophenyl)(5-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanone (210 mg, 0.54 mmol) in 4:1 MeOH/THF was added sodium borohydride (33 mg, 0.87 mmol) and the mixture was stirred for 1 h. The mixture was concentrated under a stream of air and then diluted with water. The precipitated solid was collected by filtration and washed with water, and then purified by preparative reverse phase HPLC to afford (*R, S*)-(4-fluorophenyl)(5-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanol as a white solid (49 mg, 24%). ¹H NMR (DMSO- *d*₆): δ 12.09 (s, 1H), 8.29 (s, 1H), 7.51 (t, 2H), 7.24 (s, 1H), 7.14 (t, 2H), 6.37 (s, 1H), 5.89 (s, 1H), 5.68 (d, 1H), 2.66 (s, 3H), 2.23 (s, 3H); LC-MS (ESI) *m/z* 370 (M + H)⁺.

Example 12

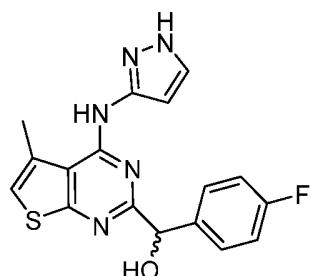
Preparation of (4-(1H-pyrazol-3-ylamino)-5-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone



[00263] A mixture of (4-chloro-5-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone from Example 10 Step C (200 mg, 0.65 mmol), 1H-pyrazol-3-amine (108 mg, 1.3 mmol), DIEA (0.16 mL, 0.91 mmol), and KI (108 mg, 0.65 mmol) was heated at 80 °C for 18 h. The mixture was diluted with water and the precipitated solid was collected by filtration, washed with water, and purified by preparative reverse phase HPLC to afford (4-(1H-pyrazol-3-ylamino)-5-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone as a white solid (94 mg, 41%). ¹H NMR (DMSO-*d*₆): δ 12.51 (s, 1H), 8.74 (s, 1H), 8.09 (t, 2H), 7.65 (s, 1H), 7.51 (s, 1H), 7.38 (t, 2H), 6.62 (s, 1H), 2.77 (s, 3H); LC-MS (ESI) *m/z* 354 (M + H)⁺.

Example 13

Preparation of (R,S)-(4-(1H-pyrazol-3-ylamino)-5-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanol

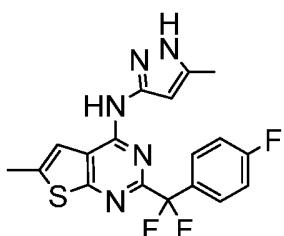


[00264] (4-(1H-pyrazol-3-ylamino)-5-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone from Example 12 (80 mg, 0.2 mmol) in 3:1 MeOH/THF (4 mL) was treated with sodium borohydride (33 mg, 0.87 mmol) and the mixture was stirred for 1 h. The mixture was concentrated under a stream of air and diluted with water. The solid was collected by filtration, washed with water, and purified by

preparative reverse phase HPLC to afford (*R,S*)-(4-(1*H*-pyrazol-3-ylamino)-5-methylthieno[2,3-*d*]pyrimidin-2-yl)(4-fluorophenyl)methanol (23 mg, 32%). ¹H NMR (DMSO-*d*₆): δ 12.45 (s, 1H), 8.44 (s, 1H), 7.68 (s, 1H), 7.52 (t, 2H), 7.24 (s, 1H), 7.12 (t, 2H), 6.78 (s, 1H), 5.88 (s, 1H), 5.68 (d, 1H), 2.68 (s, 3H); LC-MS (ESI) *m/z* 356 (M + H)⁺.

Example 14

Preparation of 2-(difluoro(4-fluorophenyl)methyl)-6-methyl-N-(5-methyl-1*H*-pyrazol-3-yl)thieno[2,3-*d*]pyrimidin-4-amine



[00265] **Step A:** To a solution of 2-amino-5-methylthiophene-3-carboxamide (1.0 mg, 6.4 mmol) in DMF (15 mL) at rt were added 2,2-difluoro-2-(4-fluorophenyl)acetic acid from Example 8 Step A (1.3 g, 7 mmol), HATU (2.67 g, 7 mmol) and diisopropylethylamine (1.45 mL, 8.3 mmol), and the mixture was stirred overnight. The mixture was diluted with water (12 mL), and the precipitated solid was collected by filtration and left under vacuum overnight to afford 2-(2,2-difluoro-2-(4-fluorophenyl)acetamido)-5-methylthiophene-3-carboxamide as an off white solid (2.10 g, 100%) which was pure enough to be used in the next step. ¹H NMR (DMSO-*d*₆): δ 13.48 (s, 1H), 8.03 (s, 1H), 7.74-7.70 (m, 3H), 7.42 (t, 2H), 7.19 (s, 1H), 2.37 (s, 3H). LC-MS (ESI) *m/z* 329 (M + H)⁺.

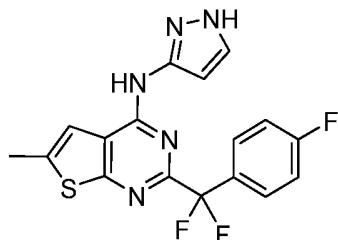
[00266] **Step B:** A mixture of 2-(2,2-Difluoro-2-(4-fluorophenyl)acetamido)-5-methylthiophene-3-carboxamide (2.1 g, 6.4 mmol), TMSCl (12.1 mL, 0.096 mol), and TEA (14 mL, 0.1 mol) in 1,2-dichloroethane (40 mL) was heated at 80 °C for 18 h. The mixture was filtered and concentrated, and the residue was subjected to aqueous workup, and the crude product was triturated with diethyl ether to afford 2-(difluoro(4-fluorophenyl)methyl)-6-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one as an off-white solid (1.14 g, 57%). ¹H NMR (DMSO-*d*₆): δ 13.32 (s, 1H), 7.72 (m, 2H), 7.38 (t, 2H), 7.16 (s, 1H); 2.52 (s, 3H); LC-MS (ESI) *m/z* 311 (M + H)⁺.

[00267] **Step C:** 2-(Difluoro(4-fluorophenyl)methyl)-6-methylthieno[2,3-d]pyrimidin-4(3H)-one (1.14 g, 3.67 mmol) in POCl_3 (30 mL) was heated at 110 °C for 6 h. The mixture was concentrated, and then toluene was added and evaporated. The residue was dissolved in DCM and filtered through a pad of silica gel eluting with DCM. The filtrate was concentrated to afford 4-chloro-2-(difluoro(4-fluorophenyl)methyl)-6-methylthieno[2,3-d]pyrimidine as a light yellow solid (1.08 g, 89%). R_f (silica gel, 3:7 ethyl acetate/hexanes): 0.7.

[00268] **Step D:** A mixture of 4-chloro-2-(difluoro(4-fluorophenyl)methyl)-6-methylthieno[2,3-d]pyrimidine (120 mg, 0.365 mmol), 5-methyl-1H-pyrazol-3-amine (42 mg, 0.44 mmol), DIEA (76 uL), and KI (61 mg, 0.36 mmol) in DMF (2 mL) was stirred at rt for 5 h and at 50 °C for 18 h. The mixture was diluted with water and the precipitated solid was collected by filtration and purified by preparative reverse phase HPLC to yield 2-(difluoro(4-fluorophenyl)methyl)-6-methyl-N-(5-methyl-1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine as a white solid (22 mg, 15%). ^1H NMR ($\text{DMSO}-d_6$): δ 12.11 (s, 1H), 10.45 (s, 1H), 7.69–7.64 (m, 3H), 7.35 (t, 2H) 6.17 (s, 1H), 2.57 (s, 3H), 2.20 (s, 3H); LC-MS (ESI) m/z 390 ($M + H$) $^+$.

Example 15

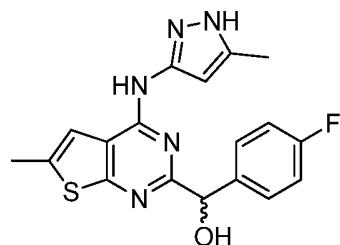
Preparation 2-(difluoro(4-fluorophenyl)methyl)-6-methyl-N-(1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine



[00269] 2-(Difluoro(4-fluorophenyl)methyl)-6-methyl-N-(1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine (12.5 mg, 9%) was prepared using a procedure analogous to that described in Example 14 Step D, substituting 3-aminopyrazole for the 5-methyl-1H-pyrazol-3-amine used in Example 14. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 2.57 (s, 3H), 6.67 (s, 1H), 7.30 – 7.36 (m, 2H), 7.65 – 7.69 (m, 4H), 10.59 (br s, 1H), 12.47 (br s, 1H); LC-MS (ESI) m/z 376 ($M + H$) $^+$.

Example 16

Preparation of (R, S)-(4-fluorophenyl)(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanol



[00270] **Step A:** To a stirred solution of 2-cyanoacetamide (4.2 g, 50 mmol), elemental sulfur (1.6 g, 50 mmol) and TEA (5.1 g, 50 mmol) in DMF at rt was added slowly a solution of propionaldehyde (3.2 g, 55 mmol) in EtOH. The reaction mixture was heated at 60 °C for 1.5 h, and then partitioned between water and EtOAc. The organic layer was separated, washed sequentially with water then brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with a mixture of DCM in MeOH to afford 2-amino-5-methylthiophene-3-carboxamide (4.1 g, 53%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.18 (s, 3H), 6.69 (s, 1H), 7.05 (s, 2H); LC-MS (ESI) *m/z* 157 (M + H)⁺.

[00271] **Step B:** To a stirred mixture of 2-amino-5-methylthiophene-3-carboxamide (156 mg, 1.0 mmol) and ethyl cyanoformate (0.11 mL, 1.1 mmol) in HOAc (1 mL) was added concentrated hydrochloric acid (0.1 mL) and the mixture was heated at 80 °C for 3 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography eluting with a mixture of DCM in MeOH to afford ethyl 6-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxylate as a brown solid (150 mg, 63%). LC-MS (ESI) *m/z* 239 (M + H)⁺.

[00272] **Step C:** A stirred mixture of ethyl 6-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-carboxylate (1.5 g, 6.3 mmol) and phosphorus oxychloride (13 mL) was heated at reflux for 2 h. The mixture was concentrated under reduced pressure and the residue was poured into ice water. The mixture was basified with saturated aq sodium hydrogen carbonate, then extracted with EtOAc. The EtOAc layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced

pressure to afford ethyl 4-chloro-6-methylthieno[2,3-d]pyrimidine-2-carboxylate (1.2 g, 75%). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.50 (t, $J = 7.2$ Hz, 3H), 2.74 (s, 3H), 4.59 (q, $J = 7.2$ Hz, 2H), 7.22 (s, 1H); LC-MS (ESI) m/z 257 ($M + H$) $^+$.

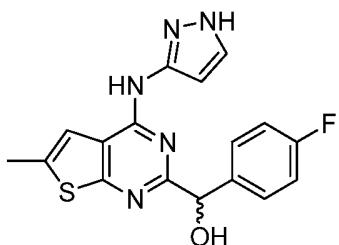
[00273] **Step D:** To a stirred solution of ethyl 4-chloro-6-methylthieno[2,3-d]pyrimidine-2-carboxylate (1.02 g, 3.98 mmol) in THF (12 mL) at -30°C was added 2M 4-fluorophenylmagnesium bromide/diethyl ether (2.39 mL, 4.78 mmol). The mixture was stirred at -30°C for 2 h. To the reaction mixture was added 1 M aq hydrochloric acid and the mixture was extracted with EtOAc. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford (4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (1.08 g). LC-MS (ESI) m/z 307 ($M + H$) $^+$.

[00274] **Step E:** To a stirred solution of (4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (153 mg, 0.5 mmol) in DMF (2 mL) were added 5-methyl-1H-pyrazol-3-amine (97 mg, 1.0 mmol) and 4M HCl/1,4-dioxane (0.5 mL, 2.0 mmol) and the mixture was heated at 90°C for 2 h. The mixture was diluted with water and the resulting solid was collected by filtration and washed with water then dried to afford crude (4-fluorophenyl)(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanone as a yellow solid (168 mg). LC-MS (ESI) m/z 368 ($M + H$) $^+$.

[00275] **Step F:** To a stirred suspension of crude (4-fluorophenyl)(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanone (168 mg) in MeOH (5 mL) was added sodium borohydride (35 mg, 0.92 mmol), and the mixture was stirred at rt for 5 min. The mixture was concentrated under reduced pressure. To the residue was added water and the resulting solid was collected by filtration and dried. The solid was further purified to afford (*R, S*)-(4-fluorophenyl)(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanol as a solid (39 mg, 21% from 4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.24 (s, 3H), 5.66 (m, 1H), 5.83 (m, 1H), 6.43 (s, 1H), 7.12 – 7.16 (m, 2H), 7.50 – 7.58 (m, 3H), 10.09 (br s, 1H), 12.04 (br s, 1H); LC-MS (ESI) m/z 370 ($M + H$) $^+$.

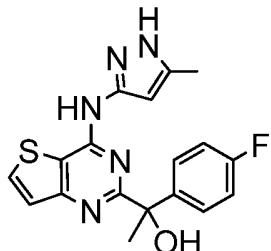
Example 17

Preparation of (R, S)-(4-(1H-pyrazol-3-ylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanol

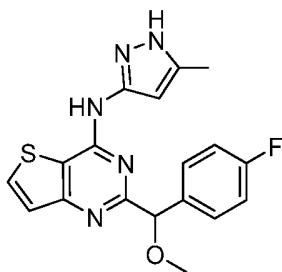


[00276] **Step A:** (4-(1H-Pyrazol-3-ylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone was prepared as a yellow solid (162 mg) using a procedure analogous to that described in Example 16 Step E, substituting 3-aminopyrazole for the 5-methyl-1H-pyrazol-3-amine used in Example 16. LC-MS (ESI) m/z 354 ($M + H$)⁺.

[00277] **Step B:** (*R, S*)-(4-(1H-Pyrazol-3-ylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanol was prepared from (4-(1H-pyrazol-3-ylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (162 mg) using a procedure analogous to that described in Example 16 Step F. Purification by chromatography afforded (*R, S*)-(4-(1H-pyrazol-3-ylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanol as a solid (35 mg, 10% from (4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.54 (s, 3H), 5.66 (m, 1H), 5.83 (m, 1H), 6.84 (s, 1H), 7.10 – 7.14 (m, 2H), 7.51 – 7.67 (m, 4H), 10.22 (br s, 1H), 12.39 (br s, 1H); LC-MS (ESI) m/z 356 ($M + H$)⁺.

Example 18**Preparation of (R,S)-1-(4-fluorophenyl)-1-(4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)ethanol**

[00278] To a solution of (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl) methanone (58 mg, 0.164 mmol) in THF (4 mL) at room temperature was added 3M methylmagnesium bromide/THF (0.33 mL, 0.98 mmol), and the mixture was stirred overnight. The mixture was concentrated under a stream of air and the residue was diluted with water. The precipitated solid was collected by filtration and purified by preparative reverse phase HPLC to afford (R,S)-1-(4-fluorophenyl)-1-(4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)ethanol as a white solid (10 mg, 16%). ¹H NMR (DMSO-*d*₆): δ 12.10 (s, 1H), 10.23 (s, 1H), 8.16 (d, 1H), 7.59 (t, 2H), 7.42 (d, 1H), 7.09 (t, 2H), 6.20 (s, 1H), 5.80 (s, 1H), 2.24 (s, 3H), 1.87 (s, 3H); LC-MS (ESI) *m/z* 370 (M + H)⁺.

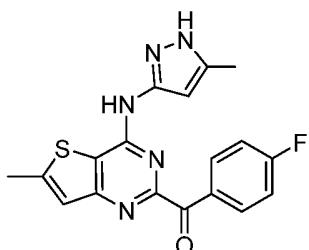
Example 19**Preparation of 2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine**

[00279] To suspension of (4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanol (118 mg, 0.33 mmol) in 1,2-dichloroethane (20 mL) was added 1M PBr₃ /DCM (0.66 mL, 0.66 mmol), and the mixture was heated at 60 °C for 1 h. The mixture was partitioned between 1,2-dichloroethane and saturated aq NaHCO₃, and then the separated organic layer was

washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was suspended in MeOH (15 mL) and heated at 60 °C for 2 h. The mixture was concentrated under reduced pressure and the residue was purified twice by preparative reverse phase HPLC to yield 2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine as a white solid (4 mg, 3%). ¹H NMR (DMSO-*d*₆): δ 12.10 (bs, 1H), 10.18 (s, 1H), 8.13 (s, 1H), 7.53 (s, 2H), 7.40 (s, 1H), 7.15 (m, 2H), 6.35 (s, 1H), 5.36 (s, 1H), 3.34 (s, 3H), 2.25 (s, 3H); LC-MS (ESI) *m/z* 370 (M + H)⁺.

Example 20

Preparation of (4-fluorophenyl)(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanone



[00280] **Step A:** To a solution of methyl 3-amino-5-methylthiophene-2-carboxylate (915 mg, 5.34 mmol) in acetic acid (6 mL) were added concentrated hydrochloric acid (0.6 mL) and methyl cyanoformate (0.466 mL, 5.88 mmol) and the mixture was heated at 90 °C for 3 h. After cooling, saturated aq NaHCO₃ was added slowly to pH ~ 5. The solid was collected by filtration, washed with water and left under vacuum overnight to afford ethyl 6-methyl-4-oxo-3,4-dihydrothieno[3,2-d]pyrimidine-2-carboxylate as a brown solid (1.09 mg, 91%). LC-MS (ESI) *m/z* 225 (M + H)⁺. To a suspension of the solid in ethanol (150 mL) was added 4 N HCl/1,4-dioxane (20 mL) and the mixture was heated at 60 °C overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in 2:1 DCM/THF, washed with saturated aq NaHCO₃ and brine, then dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with DCM/MeOH to afford ethyl 6-methyl-4-oxo-3,4-dihydrothieno[3,2-d]pyrimidine-2-carboxylate as an off white solid (180 mg, 15%). LC-MS (ESI) *m/z* 239 (M + H)⁺.

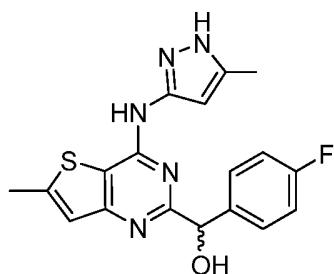
[00281] **Step B:** Ethyl 4-chloro-6-methylthieno[3,2-d]pyrimidine-2-carboxylate was obtained as a light yellow solid (120 mg, 62%) using a procedure analogous to that described in Example 20 Step C, substituting ethyl 6-methyl-4-oxo-3,4-dihydrothieno[3,2-d]pyrimidine-2-carboxylate for the 2-(difluoro(4-fluorophenyl)-7-fluoroquinazolin-4-ol used in Example 20. LC-MS (ESI) m/z 257 ($M + H$)⁺.

[00282] **Step C:** To ethyl 4-chloro-6-methylthieno[3,2-d]pyrimidine-2-carboxylate (120 mg, 0.47 mmol) in THF (3 mL) at -40 °C was added 2M 4-fluorophenylmagnesium bromide/THF (0.28 mL, 0.56 mmol) and the mixture was stirred at -40 °C for 6 h. The mixture was partitioned between EtOAc and 0.5 N HCl, and then the separated organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 9:1 hexanes/EtOAc to afford 4-chloro-6-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone as an off-white solid (128 mg, 89%). LC-MS (ESI) m/z 307 ($M + H$)⁺.

[00283] **Step D:** A mixture of (4-chloro-6-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (128 mg, 0.42 mmol), 5-methyl-1H-pyrazol-3-amine (49 mg, 0.5 mmol), DIEA (87 uL, 0.5 mmol), and KI (70 mg, 0.42 mmol) in DMF (2 mL) was heated at 80 °C overnight. The reaction mixture was diluted with water and the precipitated solid was collected by filtration, washed with H₂O, and purified by preparative reverse phase HPLC to afford (4-fluorophenyl)(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanone as a white solid (60 mg, 38%). ¹H NMR (DMSO-*d*₆): δ 12.25 (s, 1H), 10.25 (s, 1H), 8.04 (t, 2H), 7.38 (t, 2H), 7.23 (s, 1H), 6.27 (s, 1H), 2.62 (s, 3H), 2.20 (s, 3H); LC-MS (ESI) m/z 368 ($M + H$)⁺.

Example 21

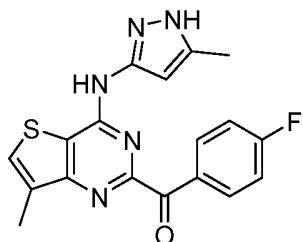
Preparation of (R,S)-(4-fluorophenyl)(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanol



[00284] To (4-fluorophenyl)(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanone (50 mg, 0.13 mmol) in MeOH (2 mL) was added sodium borohydride (8 mg, 0.21 mmol) and the mixture was stirred at rt overnight. The mixture was concentrated under a stream of air and the residual mixture was diluted with water. The precipitated solid was collected by filtration and purified by preparative reverse phase HPLC to afford (*R,S*)-(4-fluoro-phenyl)(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanol as a white solid (18 mg, 36%). ¹H NMR (DMSO-*d*₆): δ 12.14 (s, 1H), 9.97 (s, 1H), 7.50 (m, 2H), 7.16-7.08 (m, 3H), 6.22 (s, 1H), 5.76 (s, 1H), 5.64 (d, 1H), 2.57 (s, 3H), 2.23 (s, 3H); LC-MS (ESI) *m/z* 370 (M + H)⁺.

Example 22

Preparation of (4-fluorophenyl)(7-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanone



[00285] **Step A:** To a stirred mixture of methyl 3-amino-4-methylthiophene-2-carboxylate (312 mg, 2.0 mmol) and ethyl cyanoformate (0.3 mL, 3.0 mmol) in acetic acid (3.0 mL) was added concentrated hydrochloric acid (0.15 mL) and the resulting mixture was stirred at 75 °C for 3 h. After cooling to rt, the mixture was concentrated under reduced pressure and the residue was treated with EtOAc. The precipitated solid was filtered, washed with EtOAc and dried to afford ethyl 7-methyl-4-oxo-3,4-dihydrothieno[3,2-d]pyrimidine-2-carboxylate (320 mg, 67%). LC-MS (ESI) *m/z* 239 (M+H)⁺.

[00286] **Step B:** A stirred mixture of ethyl 7-methyl-4-oxo-3,4-dihydrothieno[3,2-d]pyrimidine-2-carboxylate (1 g, 4.2 mmol) in phosphorous oxychloride (15 mL) was heated at reflux for 2 h. After cooling to rt, the solvent was removed under reduced pressure. The residue was poured into ice water, neutralized, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and

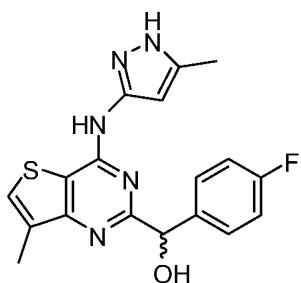
concentrated under reduced pressure to afford ethyl 4-chloro-7-methylthieno[3,2-d]pyrimidine-2-carboxylate (850 mg, 79%). LC-MS (ESI) *m/z* 257 (M+H)⁺.

[00287] Step C: To a stirred solution of ethyl 4-chloro-7-methylthieno[3,2-d]pyrimidine-2-carboxylate (850, 3.3 mmol) in anhydrous THF (15 mL) at -30 °C was added 2M 4-fluorophenylmagnesium bromide/diethyl ether (2 mL, 4.0 mmol) and the resulting mixture was stirred at -30 °C for 1 h. The mixture was diluted with 2N HCl and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford (4-chloro-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (860 mg, 85%). LC-MS (ESI) *m/z* 307 (M+H)⁺.

[00288] Step D: To a stirred solution of (4-chloro-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (93 mg, 0.3 mmol) in DMF (3 mL) were added 3-methyl-1H-pyrazol-5-amine (97 mg, 1.0 mmol) and 4M HCl/1,4-dioxane (0.2 mL, 0.8 mmol) and the mixture was stirred at 90 °C for 15 h. After this time, additional 3-methyl-1H-pyrazol-5-amine (97 mg, 1.0 mmol) and 4M HCl/1,4-dioxane (0.5 mL) were added and the mixture was heated in a microwave synthesizer at 140 °C for 45 min. The mixture was then poured into water and the precipitated solid was collected by filtration and purified by silica gel chromatography to afford (4-fluorophenyl)(7-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanone as a solid (33 mg, 30%). ¹H NMR (300 MHz, DMSO-d₆) δ 12.24 (s, 1H), 10.31 (s, 1H), 8.07-8.11 (m, 2H), 7.91 (s, 1H), 7.39 (t, *J* = 8.8 Hz, 2H), 6.32 (s, 1H), 2.36 (s, 3H), 2.20 (s, 3H); LC-MS (ESI) *m/z* 368 (M+H)⁺.

Example 23

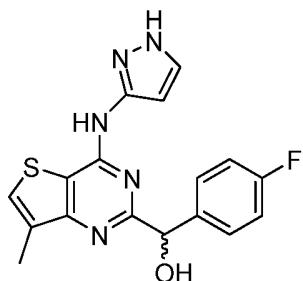
Preparation of (4-fluorophenyl)(7-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanol



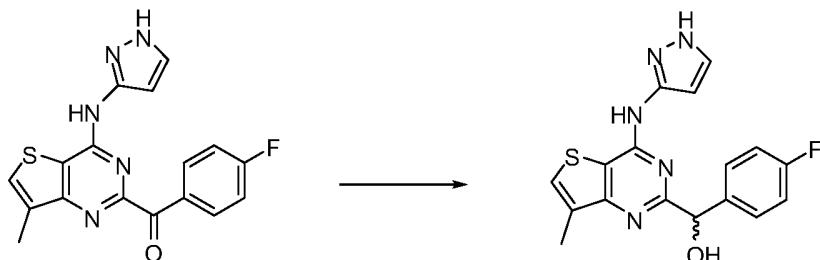
[00289] To a suspension of (4-fluorophenyl)(7-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanone, prepared as described in Example 23 Steps A through D, (160 mg, 0.44 mmol) in MeOH (10 mL) was added sodium borohydride (38 mg, 1.0 mmol) and the resulting mixture was stirred at rt for 30 minutes. The solvent was removed under reduced pressure and the residue was treated with water. The precipitated solid was collected by filtration, washed with water and diethyl ether, and dried. The crude product was recrystallized from MeOH/diethyl ether to afford (4-fluorophenyl)(7-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanol (100 mg, 61%). ^1H NMR (300 MHz, DMSO-d₆) δ 11.30 (s, 1H), 8.01 (s, 1H), 7.58 (t, J = 8.4 Hz, 2H), 7.19 (t, J = 8.4 Hz, 2H), 6.20 (s, 1H), 5.91 (s, 1H), 2.41 (s, 3H), 2.27 (s, 3H); LC-MS (ESI) *m/z* 370 (M+H)⁺.

Example 24

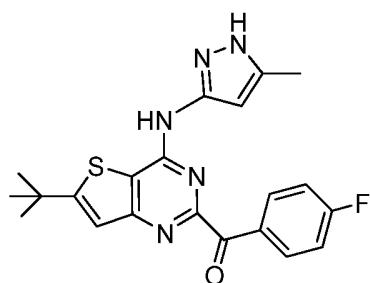
Preparation of (4-(1H-pyrazol-3-ylamino)-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol



[00290] To a stirred mixture of (4-chloro-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (93 mg, 0.3 mmol) and 1H-pyrazol-3-amine (83 mg, 1.0 mmol) in 2-methoxyethanol (3 mL) was added 4M HCl/1,4-dioxane (0.2 mL) and the mixture was heated in a microwave synthesizer at 140 °C for 60 min. The mixture was poured into water and the precipitated solid was collected by filtration and purified by silica gel chromatography to afford (4-(1H-pyrazol-3-ylamino)-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (20 mg, 19%). ^1H NMR (300 MHz, DMSO-d₆) δ 8.10 (t, J = 8.8 Hz, 2H), 7.89 (s, 1H), 7.60 (br s, 1H), 7.39 (t, J = 8.8 Hz, 2H), 6.51 (br s, 1H), 5.44 (br s, 1H), 2.36 (s, 3H); LC-MS (ESI) *m/z* 354 (M+H)⁺.

Example 25**Preparation of (4-(1H-Pyrazol-3-ylamino)-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol**

[00291] (4-(1H-Pyrazol-3-ylamino)-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol (100 mg) was prepared using a procedure analogous to that described in Example 24, substituting (4-(1H-pyrazol-3-ylamino)-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone for the (4-fluorophenyl)(7-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanone used in Example 24. ^1H NMR (300 MHz, DMSO- d_6) δ 12.50 (s, 1H), 10.24 (s, 1H), 7.80 (s, 1H), 7.69 (s, 1H), 7.55 ($t, J = 7.6$ Hz, 2H), 7.13 ($t, J = 8.8$ Hz, 2H), 6.68 (s, 1H), 5.83 (s, 1H), 5.72 (s, 1H), 2.37 (s, 3H); LC-MS (ESI) m/z 354 ($M+\text{H}^+$).

Example 26**Preparation of (6-tert-butyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl) methanone**

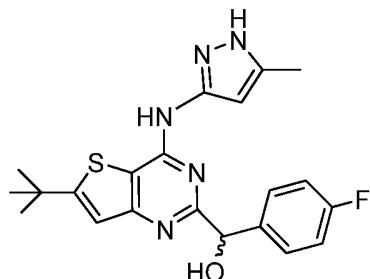
[00292] **Step A:** To 3-amino-5-tert-butylthiophene-2-carboxamide (0.60 g, 3 mmol) in acetic acid (3 mL) were added concentrated hydrochloric acid (0.3 mL) and ethyl cyanoformate (0.36 mL, 3.63 mmol) and the mixture was heated at 80 °C for 3 h. After cooling, the mixture was diluted with water and saturated aq NaHCO₃ was added to pH ~ 5. The precipitated solid was collected by filtration, washed with water, and dried under vacuum overnight to afford ethyl 6-tert-butyl-4-oxo-3,4-dihydrothieno[3,2-d]pyrimidine-2-carboxylate as a white solid (790 mg, 94%). ^1H

NMR (DMSO-*d*₆): δ 12.82 (s, 1H), 7.30 (s, 1H), 4.35 (q, 2H), 1.32 (s, 9H), 1.30 (t, 3H).

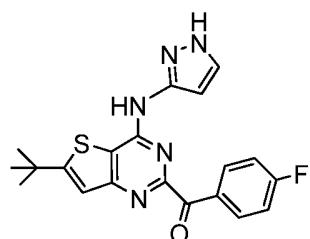
[00293] **Step B:** A mixture of ethyl 6-tert-butyl-4-oxo-3,4-dihydrothieno[3,2-d]pyrimidine-2-carboxylate (790 mg, 2.82 mmol) in POCl₃ (10 mL) was heated at 105 °C for 6 h. The mixture was concentrated under reduced pressure, and then toluene was added and evaporated. The residue was dissolved in DCM and passed through a pad of silica gel eluting with DCM. The filtrate was concentrated under reduced pressure to afford ethyl 6-tert-butyl-4-chlorothieno[3,2-d]pyrimidine-2-carboxylate as a light yellow solid (650 mg, 77%). LC-MS (ESI) *m/z* 249 (M + H)⁺.

[00294] **Step C:** tert-Butyl-4-chlorothieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone was prepared as an off-white solid (604 mg, 63%) using a procedure analogous to that described in Example 21 Step C, substituting ethyl 6-tert-butyl-4-chlorothieno[3,2-d]pyrimidine-2-carboxylate for the ethyl 4-chloro-6-methylthieno[3,2-d]pyrimidine-2-carboxylate used in Example 21. LC-MS (ESI) *m/z* 349 (M + H)⁺.

[00295] **Step D:** A mixture of (6-tert-butyl-4-chlorothieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (320 mg, 0.92 mmol), 5-methyl-1H-pyrazol-3-amine (178 mg, 1.84 mmol), DIEA (223 uL, 1.29 mmol), and KI (152 mg, 0.92 mmol) in DMF (4 mL) was heated at 80 °C for 18 h. The reaction mixture was diluted with water (10 mL), and the supernatant solution was decanted. The residue was triturated with MeOH to give a solid that was collected by filtration to afford (6-tert-butyl-4-(5-methyl-1H-pyrazol-3-ylamino) thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone as a light yellow solid (330 mg, 90%). ¹H NMR (DMSO-*d*₆): 12.10 (s, 1H), 10.30 (s, 1H), 8.05 (t, 2H), 7.38 (t, 2H), 7.32 (s, 1H), 6.29 (s, 1H), 2.19 (s, 3H), 1.42 (s, 9H); LC-MS (ESI) *m/z* 410 (M + H)⁺.

Example 27**Preparation of (6-tert-butyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol**

[00296] To (6-tert-Butyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl) methanone (240 mg, 0.5 mmol) in 5:1 MeOH/THF (12 mL) was added sodium borohydride (29 mg, 0.75 mmol) and the mixture was stirred at rt for 3 h. The mixture was concentrated under a stream of air and the residue was diluted with water. The precipitated solid was collected by filtration, washed with water, and purified by preparative reverse phase HPLC to afford (6-tert-butyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol as a white solid (21 mg, 10%). ^1H NMR (DMSO- d_6): δ 12.11 (s, 1H), 9.98 (s, 1H), 7.50 (t, 2H), 7.19 (s, 1H), 7.12 (t, 2H), 6.28 (s, 1H), 5.72 (s, 1H), 5.65 (s, 1H), 1.39 (s, 9H); LC-MS (ESI) m/z 412 ($M + H$) $^+$.

Example 28**Preparation of (4-(1H-pyrazol-3-ylamino)-6-tert-butylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone**

[00297] A mixture of (6-tert-butyl-4-chlorothieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (320 mg, 0.92 mmol), 1H-pyrazol-3-amine (153 mg, 1.84 mmol), DIEA (223 uL, 1.29 mmol), and KI (152 mg, 0.92 mmol) in DMF (4 mL) was heated at 80 °C for 18 h. The reaction mixture was diluted with water, and the precipitated solid was collected by filtration, washed with water, and then triturated

with MeOH to afford (6-tert-butyl-4-(5-methyl-1H-pyrazol-3-ylamino) thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone as a light yellow solid (350 mg, 90%). LC-MS (ESI) m/z 396 ($M + H$)⁺.

Example 29

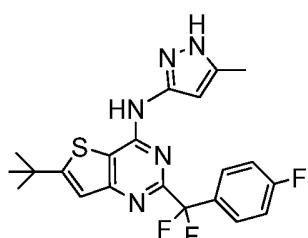
Preparation of (R,S)-(4-(1H-pyrazol-3-ylamino)-6-tert-butylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol



[00298] To (4-(1H-pyrazol-3-ylamino)-6-tert-butylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone (217 mg, 0.5 mmol) in 5:1 MeOH/THF (12 mL) was added sodium borohydride (29 mg, 0.75 mmol) and the mixture was stirred at rt for 3 h. The mixture was concentrated under a stream of air and diluted with water. The precipitated solid was collected by filtration, washed with water, and purified by preparative reverse phase HPLC to yield (R,S)-(4-(1H-pyrazol-3-ylamino)-6-tert-butylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol as a white solid (21 mg, 11%). ^1H NMR (DMSO- d_6): δ 12.46 (s, 1H), 10.11 (s, 1H), 7.67 (s, 1H), 7.50 (t, 2H), 7.20 (s, 1H), 7.11 (t, 2H), 6.64 (s, 1H), 5.74 (s, 1H), 5.67 (s, 1H) 1.39 (s, 9H); LC-MS (ESI) m/z 398 ($M + H$)⁺.

Example 30

Preparation of 6-tert-butyl-2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine



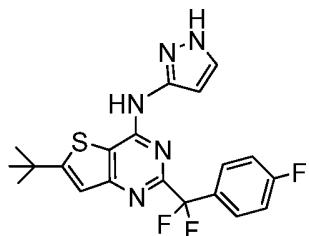
[00299] **Step A:** To a solution of 3-amino-5-tert-butylthiophene-2-carboxamide (500 mg, 2.52 mmol) in DMF (5 mL) at rt were added 2,2-difluoro-2-(4-

fluorophenyl)acetic acid from Example 8 Step A (528 mg, 2.77 mmol), HATU (1.05 g, 2.77 mmol), and diisopropylethylamine (0.48 mL, 2.77 mmol), and the mixture was stirred overnight. The mixture was diluted with water (12 mL) and the supernatant solution was decanted. The residue was dissolved in EtOAc, dried over MgSO₄, filtered, and concentrated under reduced pressure to afford 5-tert-butyl-3-(2,2-difluoro-2-(4-fluorophenyl)acetamido)thiophene-2-carboxamide as an off white solid (1.02 g, 100%). LC-MS (ESI) *m/z* 271 (M + H)⁺.

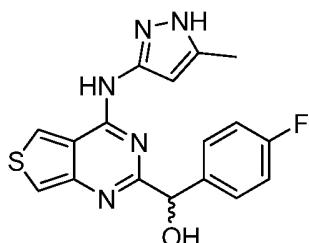
[00300] **Step B:** 6-tert-Butyl-2-(difluoro(4-fluorophenyl)methyl)thieno[3,2-d]pyrimidin-4(3H)-one was obtained as an off white solid (808 mg, 85%) using a procedure analogous to that described in Example 20 Step B, substituting 5-tert-butyl-3-(2,2-difluoro-2-(4-fluorophenyl)acetamido)thiophene-2-carboxamide for the 2-(2,2-difluoro-2-(4-fluorophenyl)acetamido)-4-fluorobenzamide used in Example 20. ¹H NMR (DMSO-*d*₆): δ 13.20 (bs, 1H), 7.74 (t, 2H), 7.38 (t, 2H), 7.30 (s, 1H), 1.38 (s, 9H).

[00301] **Step C:** 6-Tert-butyl-4-chloro-2-(difluoro(4-fluorophenyl)methyl)thieno[3,2-d]pyrimidine was prepared as a pale yellow solid (380 mg, 45%) using a procedure analogous to that described in Example 20 Step C, substituting 6-tert-butyl-2-(difluoro(4-fluorophenyl)methyl)thieno[3,2-d]pyrimidin-4(3H)-one for the 2-(difluoro(4-fluorophenyl)-7-fluoroquinazolin-4-ol used in Example 20. TLC (silica gel) R_f (3:7 ethyl acetate/hexanes): 0.7.

[00302] **Step D:** A mixture of 6-tert-butyl-4-chloro-2-(difluoro(4-fluorophenyl)methyl)thieno[3,2-d]pyrimidine (180 mg, 0.51 mmol), 5-methyl-1H-pyrazol-3-amine (99 mg, 1.02 mmol), DIEA (124 uL, 0.71 mmol), and KI (85 mg, 0.51 mmol) was stirred at 80 °C and then at rt overnight. The crude product was purified by preparative reverse phase HPLC to afford 6-tert-butyl-2-(difluoro(4-fluorophenyl) methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine as a white solid (47 mg, 21%). ¹H NMR (DMSO-*d*₆): δ 12.14 (s, 1H), 10.36 (s, 1H), 7.65 (t, 2H), 7.36-732 (m, 3H), 6.15 (s, 1H), 2.22 (s, 3H), 1.40 (s, 9H); LC-MS (ESI) *m/z* 432 (M + H)⁺.

Example 31**Preparation of 6-tert-butyl-2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine**

[00303] 6-tert-Butyl-2-(difluoro(4-fluorophenyl)methyl) -N-(1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine was prepared as a white solid (12 mg, 6%) using a procedure analogous to that described in Example 31 Step D, substituting 1H-pyrazol-3-amine for the 5-methyl-1H-pyrazol-3-amine used in Example 31. ¹H NMR (DMSO-*d*₆): δ 12.53 (s, 1H), 10.46 (s, 1H), 7.70-7.63 (m, 3H), 7.34-7.29 (m, 3H), 6.58 (s, 1H), 1.39 (s, 9H); LC-MS (ESI) *m/z* 418 (M + H)⁺.

Example 32**Preparation (*R,S*)-(4-fluorophenyl)(4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,4-d]pyrimidin-2-yl)methanol**

[00304] **Step A:** A stirred mixture of methyl 4-aminothiophene-3-carboxylate (1.9 g, 12 mmol), ethyl carbonocyanide (2.37 mL, 24 mmol) and concentrated hydrochloric acid (1.5 mL) in HOAc (15 mL) was heated at 70 °C for 4 h to afford after isolation ethyl 4-hydroxythieno[3,4-d]pyrimidine-2-carboxylate (1.2 g, 45%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.34 (t, *J* = 6.9 Hz, 3H), 4.36 (q, *J* = 6.9 Hz, 2H), 8.14 (s, 1H), 8.57 (s, 1H), 11.97 (br s, 1H).

[00305] **Step B:** A stirred mixture of ethyl 4-hydroxythieno[3,4-d]pyrimidine-2-carboxylate (1.18 g, 5.27 mmol) and phosphorus oxychloride (20 mL) was heated at 105 °C for 12 h. Following workup in the usual manner, the mixture was purified by filtration through a plug of silica gel eluting with DCM to afford ethyl 4-

chlorothieno[3,4-d]pyrimidine-2-carboxylate (750 mg, 59%). LC-MS (ESI) *m/z* 243 (M + H)⁺.

[00306] **Step C:** To stirred mixture of ethyl 4-chlorothieno[3,4-d]pyrimidine-2-carboxylate (750 mg, 3.11 mmol) in THF (45 mL) at -40 °C was added 1M (4-fluorophenyl)magnesium bromide/THF (4.04 mL, 4.04 mmol). The mixture was stirred at -40 to -30 °C for 15 h. After the usual workup, the resulting mixture was purified by silica gel chromatography eluting with EtOAc/hexanes to afford (4-fluorophenyl)(4-hydroxythieno[3,4-d]pyrimidin-2-yl)methanone as a solid (200 mg, 24%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 7.42 (m, 2H), 8.12 (s, 1H), 8.25 (m, 2H), 8.60 (s, 1H), 12.02 (br s, 1H). LC-MS (ESI) *m/z* 275 (M + H)⁺.

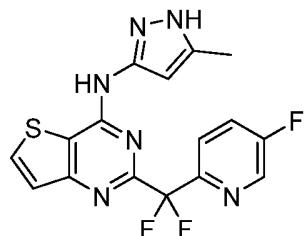
[00307] **Step D:** A stirred mixture of (4-fluorophenyl)(4-hydroxythieno[3,4-d]pyrimidin-2-yl)methanone (200 mg, 0.73 mmol) and phosphorus oxychloride (5 mL) was heated at 105 °C for 2 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography eluting with 10% MeOH /DCM to afford a mixture of products, which was heated with phosphorus oxychloride (5 mL) at 100 °C for 2 h. The mixture was concentrated under reduced pressure to afford (4-fluorophenyl)(4-methoxythieno[3,4-d]pyrimidin-2-yl)methanone (380 mg) which was used directly in the next step. LC-MS (ESI) *m/z* 289 (M + H)⁺.

[00308] **Step E:** A mixture of (4-fluorophenyl)(4-methoxythieno[3,4-d]pyrimidin-2-yl)methanone (380 mg), 5-methyl-1*H*-pyrazol-3-amine (150 mg, 1.55 mmol) and DIEA (0.4 mL, 2.3 mmol) in DMF (4 mL) was stirred at rt to afford (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)thieno[3,4-d]pyrimidin-2-yl)methanone. The obtained (4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)thieno[3,4-d]pyrimidin-2-yl)methanone was added to a mixture of MeOH (6 mL) and THF (2 mL), and to this was added sodium borohydride (23 mg, 0.62 mmol). The mixture was stirred for 1 h. The mixture was concentrated, diluted with water (6 mL) and extracted with a mixture of EtOAc and THF. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified to afford (*R,S*)-(4-fluorophenyl)(4-(5-methyl-1*H*-pyrazol-3-ylamino)thieno[3,4-d]pyrimidin-2-yl)methanol as a solid (3 mg, 1% from (4-fluorophenyl)(4-hydroxythieno[3,4-d]pyrimidin-2-yl)methanone). LC-MS (ESI)

single peak m/z 356 ($M + H$)⁺. ^1H NMR (300 MHz, DMSO-*d*₆) was consistent with the product plus one or more impurities or tautomers; key resonances include δ 2.25 (s, 3H), 5.55 (s, 1H), 7.52 – 7.60 (m, 2H).

Example 33

Preparation 2-(difluoro(5-fluoropyridin-2-yl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine



[00309] **Step A:** To a mixture of 2-bromo-5-fluoropyridine (2 g, 11.36 mmol), and ethyl 2-bromo-2,2-difluoroacetate (1.6 mL, 12.5 mmol) in DMSO (4 mL) was added copper powder (1.6 g, 24.98 mmol) and the mixture was stirred at 50 °C overnight in a sealed flask. The crude mixture was diluted with DMSO (10 mL) and filtered through Celite. Then water and EtOAc were added and the mixture was shaken and again filtered through Celite. The organic layer was separated and washed with water (1X) and brine (1X) and dried over sodium sulfate. The solution was concentrated to afford ethyl 2,2-difluoro-2-(5-fluoropyridin-2-yl)acetate as a yellow oil (1.5 g, 60%). ^1H NMR (300 MHz, CDCl₃) δ 1.34 (t, 3H) 4.38 (q, 2H) 7.56 (dt, 1H) 7.77 (dd, 1H) 8.50 (d, 1H).

[00310] **Step B:** To ethyl 2,2-difluoro-2-(5-fluoropyridin-2-yl)acetate (560 mg, 2.55 mmol) in 1:1 MeOH/THF (10mL) at rt was added 1 M NaOH (2.8 mL, 2.8 mmol), and the solution was stirred for 10 min and then concentrated to dryness to afford crude sodium 2,2-difluoro-2-(5-fluoropyridin-2-yl)acetate (548 mg, quantitative). ^1H NMR (300 MHz, DMSO-*d*₆) δ 7.66 (dd, 1H) 7.79 (dt, 2H) 8.54 (d, 1H).

[00311] **Step C:** To 3-aminothiophene-2-carboxamide (350 mg, 2.46 mmol) and sodium 2,2-difluoro-2-(5-fluoropyridin-2-yl)acetate (630 mg, 2.95 mmol) was added trimethylsilyl polyphosphate (~ 5 mL) and the resulting solution was heated at 115 °C overnight. EtOAc and water were added and the mixture was stirred for 30 min. The organic layer was dried over sodium sulfate and then concentrated under reduced

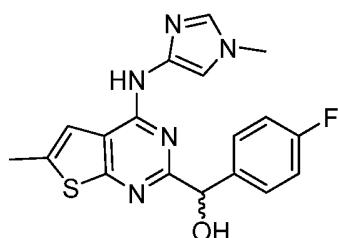
pressure. The residue was purified by silica gel chromatography eluting with 0-10% MeOH/DCM to afford 2-(difluoro(5-fluoropyridin-2-yl)methyl)thieno[3,2-d]pyrimidin-4-ol (330 mg, 45%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.58 (s, 1H), 8.74 (s, 1H), 7.86 - 8.16 (m, 3H), 7.31 (d, *J* = 5.3 Hz, 1H).

[00312] **Step D:** To 2-(difluoro(5-fluoropyridin-2-yl)methyl)thieno[3,2-d]pyrimidin-4-ol (150 mg, 0.5 mmol) was added phosphorous oxychloride (3 mL) and the mixture heated at 90 °C overnight. The solution was allowed to cool to rt and then DIEA (0.18 mL, 1 mmol) was added and the reaction mixture was heated to 105 °C for 4 h and then 95 °C for 3 days. The mixture was concentrated under reduced pressure and then toluene (5 mL) was added and evaporated. The residue was then purified by silica gel chromatography eluting with 0-8%MeOH/DCM to afford 4-chloro-2-(difluoro(5-fluoropyridin-2-yl)methyl)thieno[3,2-d]pyrimidine (130 mg, 82%). LC-MS (ESI) *m/z* 316 (M + H)⁺.

[00313] **Step E:** To a solution of 5-methyl-1H-pyrazol-3-amine (80 mg, 0.82 mmol), KI (100 mg, 0.6 mmol), and DIEA (0.083 mL, 0.47 mmol) in DMF (2 mL) was added 4-chloro-2-(difluoro(5-fluoropyridin-2-yl)methyl)thieno[3,2-d]pyrimidine (60 mg, 0.19 mmol) and the mixture was stirred at rt overnight and then at 60 °C overnight. The crude mixture was purified by preparative HPLC (Varian diphenyl reverse phase column eluted with gradient of solvent B = 0.05% HOAC/ACN and solvent A = 0.05% HOAc/H₂O) to afford 2-(difluoro(5-fluoropyridin-2-yl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine (35 mg, 47%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.20 (br s, 1H), 10.52 (br s, 1H), 8.65 (s, 1H), 8.26 (d, *J* = 5.5 Hz, 1H), 7.98 (d, *J* = 5.5 Hz, 2H), 7.50 (d, *J* = 5.5 Hz, 1H), 5.95 (s, 1H), 2.19 (s, 3H); LC-MS (ESI) *m/z* 377 (M + H)⁺.

Example 34

Preparation of (4-fluorophenyl)(6-methyl-4-(1-methyl-1H-imidazol-4-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanol



[00314] **Step A:** To (4-chloro-6-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone from Example 21 Step C (153 mg, 0.5 mmol) in DMF (2 mL) were added 1-methyl-1H-imidazol-4-amine (194 mg, 2 mmol) and DIEA (0.17 mL, 1 mmol) and the mixture was heated at 90 °C for 2 h. The mixture was diluted with water and the precipitate was collected by filtration to afford (4-fluorophenyl)(6-methyl-4-(1-methyl-1H-imidazol-4-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanone as a yellow solid (134 mg, 73%). LC-MS (ESI) *m/z* 368 (M + H)⁺.

[00315] **Step B:** (4-Fluorophenyl)(6-methyl-4-(1-methyl-1H-imidazol-4-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanol was prepared using a procedure analogous to that described in Example 22, substituting (4-fluorophenyl)(6-methyl-4-(1-methyl-1H-imidazol-4-ylamino)thieno[2,3-d]pyrimidin-2-yl)methanone for the (4-fluorophenyl)(6-methyl-4-(5-methyl-1H-pyrazol-3-ylamino)thieno[3,2-d]pyrimidin-2-yl)methanone used in Example 22. ¹H NMR (DMSO-*d*₆): δ 2.51 (d, J = 6.4 Hz, 3H), 4.65 (s, 3H), 5.72 (d, J = 4.8 Hz, 1H), 5.89 (d, J = 4.8 Hz, 1H), 7.17 (m, 2H) 7.31 (s, 1H), 7.43 (s, 1H), 7.55 (m, 2H), 7.63 (s, 1H), 10.16 (s, 1H); LC-MS (ESI) *m/z* 370 (M + H)⁺.

Example 35

Competition binding assay to determine binding constants (K_d) of the compounds against JAK kinases

[00316] Competition binding assays used herein were developed, validated and performed as described in Fabian *et al.*, *Nature Biotechnology* **2005**, 23,329-336. Kinases were produced as fusions to T7 phage (*See*, Fabian *et al.* or WO04/015142) or alternatively, the kinases were expressed in HEK-293 cells and subsequently tagged with DNA for PCR detection (*See*, WO08/005310). For the binding assays, streptavidin-coated magnetic beads were treated with biotinylated affinity ligands for 30 min at rt to generate affinity resins. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1 % BSA, 0.05 % Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific binding. Binding reactions were assembled by combining kinase, liganded affinity beads, and test compounds in 1 x binding buffer (20 % SeaBlock, 0.17x PBS, 0.05 % Tween 20, 6 mM DTT). Test compounds were prepared as 100 x stocks in DMSO and rapidly diluted into the aqueous environment. DMSO was added to control assays lacking a test compound. Primary screen interactions were performed in polypropylene 384-

well plates in a final volume of 34 µL, while Kd determinations were performed in polystyrene 96-well plates in a final volume of 135 µL. The assay plates were incubated at room temperature with shaking for 1 hour, long enough for binding reactions to reach equilibrium, and the affinity beads were washed extensively with wash buffer (1x PBS, 0.05 % Tween 20) to remove unbound protein. The beads were then resuspended in elution buffer (1x PBS, 0.05 % Tween 20, 2 µM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 min. The kinase concentration in the eluates was measured by quantitative PCR. Each kinase was tested individually against each compound. Kds were determined using eleven serial threefold dilutions. A selectivity score, which is a quantitative measure of selectivity of a compound against a panel of enzymes, may be calculated for a compound by dividing the number of enzymes for which a compound meets a set criteria, (for example, a binding constant of 100 nM or less), by the total number of enzymes tested. A kinase selectivity score, S10, for example, is calculated for each compound by dividing the number of kinases for which a compound at a certain concentration (for example, 10 µM) displayed inhibition of 90% or greater compared to negative control lacking inhibitors (DMSO only), divided by the number of distinct kinases tested excluding mutant variants, typically 359 or 386 kinases.

[00317] In one embodiment, the compounds provided herein were found to have Kds of less than about 20 µM against JAK2. In another embodiment, the compounds provided herein were found to have Kds of less than about 10 µM against JAK2. In another embodiment, the compounds provided herein were found to have Kds of less than about 1 µM against JAK2.

[00318] In another embodiment, the compounds provided herein were found to have Kds of less than about 20 µM against JAK3. In another embodiment, the compounds provided herein were found to have Kds of less than about 10 µM against JAK3. In another embodiment, the compounds provided herein were found to have Kds of less than about 1 µM against JAK3.

Example 36

CSTF-1 cell-based reporter assay

[00319] CSTF-1 cells are derived from the human erythroleukemia cell line that is growth dependent on GM-CSF and has an intact GM-CSFR/JAK2/STAT5 pathway.

The cell line contains stably integrated beta-lactamase reporter gene under the control of the regulatory factor 1 (irf 1) response element recognized by the activated transcription factor STAT5. csTF-1 cells (Invitrogen K1219) were washed with assay media (97%OPTIMEM/ 0.5%dialyzed FBS/ 0.1mM NEAA/ 1mM Na pyr/ P/S) and seeded in the same media at 5×10^5 cell/mL in T150 flask. After 16 hour incubation, cells were seeded at 2×10^5 cell/well in 50 μ L volume, into Costar, clear bottom, 96-well assay plates. Serial dilutions of compounds were added to the plates with final DMSO concentration at 0.5% and GM-CSF at 2ng/mL and the plates were then incubated at 30°C and 5% CO₂ for 4 hours. The plates were brought to room temperature before adding Substrate Mixture according to manufacturer's protocol (Invitrogen, Catalog # K1085). The assay plates containing the substrate mixture were incubated in the dark at room temperature for 2 hours. Blue and green fluorescence was measured with excitation at 409nm and emission at 460nm (for blue) and excitation at 409nm and emission at 530nm (for green) using Spectra Max Gemini EM. The compounds provided herein were found to have IC₅₀ of less than about 5 μ M. In another embodiment, the compounds provided herein were found to have activity IC₅₀ of less than about 500 nM.

[00320] The compounds provided herein were found to have the following activity shown in Table 1:

Table 1

Example	Cell Assay: CS TF-1 reporter assay IC ₅₀ (nM)	Binding Assay: JAK2 Kd (nM)	Binding Assay: JAK3 Kd (nM)	Binding Assay: TYK2 Kd (nM)	S- Score: S(10) at 10 μ M
Example 1	A	A	A	A	B
Example 2	A	A	B	A	A
Example 3	A	A	A	B	B
Example 4	A	A	A	A	B
Example 5	A	A	A	B	A
Example 6	A	A	A	A	A
Example 7	A	A	A	A	C
Example 8	A	A	B	A	A
Example 9	B	A	B	A	A
Example 10	C	C	C	C	A
Example 11	C	C	C	C	A

Example	Cell Assay: CS TF-1 reporter assay IC_{50} (nM)	Binding Assay: JAK2 Kd (nM)	Binding Assay: JAK3 Kd (nM)	Binding Assay: TYK2 Kd (nM)	S- Score: S(10) at 10 μ M
Example 12	C	C	C	C	A
Example 13	C	C	C	C	A
Example 14	A	A	B	A	A
Example 15	B	B	B	C	A
Example 16	A	A	B	A	C
Example 17	B	A	B	C	A
Example 18	A	A	A	A	A
Example 19	B	B	B	B	A
Example 20	A	A	A	B	B
Example 21	A	A	A	A	B
Example 22	B	B	C	C	A
Example 23	B	A	B	A	A
Example 24	C	B	C	C	A
Example 25	B	B	B	A	A
Example 26	B	B	C	C	A
Example 27	B	A	B	C	A
Example 28	B	B	C	C	A
Example 29	B	B	C	C	A
Example 30	B	B	B	C	A
Example 31	B	B	C	C	A
Example 32	A	A	A	A	B
Example 33	A	A	A	A	C
Example 34	B	A	C	ND	A

In Table 1,

CSTF-1 reporter assay IC_{50} (nM): A \leq 100, 100 $<$ B \leq 500, C $>$ 500;

JAK2 Kd (nM): A \leq 1, 1 $<$ B \leq 10, C $>$ 10; JAK3 Kd (nM): A \leq 10, 10 $<$ B \leq 100, C $>$ 100;

TYK2 Kd (nM) A \leq 10, 10 $<$ B \leq 100, C $>$ 100;

S score: A \leq 0.3, 0.3 $<$ B \leq 0.4, 0.4 $<$ C \leq 0.5, D $>$ 0.5; and ND= no data.

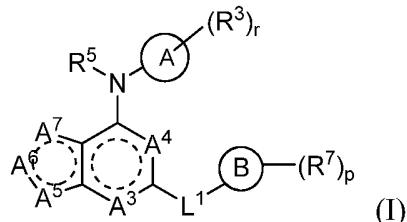
[00321] In certain embodiments, the compounds provided herein bind to JAK2 kinase with higher specificity as compared to non-mutant and non-JAK family kinases. For certain compounds provided herein, binding constants for less than 10 non-mutant and non-JAK family kinases are within 100-fold of the binding constant for JAK2 kinase for compounds provided herein. For certain compounds provided herein, binding constants for less than 8 non-mutant and non-JAK family kinases are

within 100-fold of the binding constant for JAK2 kinase for compounds provided herein. For certain compounds provided herein, binding constants for 6 non-mutant and non-JAK family kinases are within 100-fold of the binding constant for JAK2 kinase.

[00322] Since modifications will be apparent to those of skill in the art, it is intended that the claimed subject matter be limited only by the scope of the appended claims.

What is claimed is:

1. A compound having formula (I):



or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

A is azolyl;

B is aryl or heteroaryl;

A^3 and A^4 are selected from N and CR^{6a}, such that at least one of A^3 and A^4 is

N;

A^5 , A^6 , and A^7 are selected from S and CR⁶, such that one of A^5 , A^6 , or A^7 is S and the others are CR⁶;

L^1 is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R¹ and R² are selected from (i), (ii), (iii), (iv) and (v) as follows:

(i) R¹ and R² together form =O, =S, =NR⁹ or =CR¹⁰R¹¹;

(ii) R¹ and R² are both -OR⁸, or R¹ and R², together with the carbon atom to which they are attached, form cycloalkyl or heterocyclyl wherein the cycloalkyl is substituted with one to four substituents selected from halo, deutero, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cyano, =O, =N-OR²¹, -R^xOR²¹, -R^xN(R²²)₂, -R^xS(O)_qR²³, -C(O)R²¹, -C(O)OR²¹ and -C(O)N(R²²)₂ and wherein the heterocyclyl contains one to two heteroatoms wherein each heteroatom is independently selected from O, NR²⁴, S, S(O) and S(O)₂;

(iii) R¹ is hydrogen or halo; and R² is halo;

(iv) R¹ is alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl is optionally substituted with one to four substituents selected from halo, cyano, alkyl, -R^xOR^w, -R^xS(O)_qR^v, -R^xNR^yR^z and -C(O)OR^w; and R² is hydrogen, halo or -OR⁸; and

(v) R¹ is halo, deutero, -OR¹², -NR¹³R¹⁴, or -S(O)_qR¹⁵; and R² is hydrogen, deutero, alkyl, alkenyl, alkynyl, cycloalkyl or aryl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and aryl are each optionally substituted with one, two or

three, substitutents selected from halo, cyano, alkyl, -R^xOR^w, -R^xS(O)_qR^v and -R^xNR^yR^z;

each R³ is independently hydrogen, deuterio, halo, alkyl, cyano, haloalkyl, deuteroalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy;

R⁵ is hydrogen or alkyl;

each R⁶ is independently selected from hydrogen, deuterio, halo, cyano, nitro, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -R^xOR¹⁸, -R^xNR¹⁹R²⁰, -R^xC(O)NR^yR^z, -R^xS(O)_qR^v, -R^xNR¹⁹C(O)R¹⁸, -R^xC(O)OR¹⁸ and -R^xNR¹⁹S(O)_qR^v; where the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl groups are optionally substituted with one, two or three halo, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, haloalkyl, or cycloalkyl groups;

each R^{6a} is independently hydrogen, cyano or alkyl;

each R⁷ is independently halo, alkyl, haloalkyl or -R^xOR^w;

R⁸ is alkyl, alkenyl or alkynyl;

R⁹ is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy or amino;

R¹⁰ is hydrogen or alkyl;

R¹¹ is hydrogen, alkyl, haloalkyl or -C(O)OR⁸;

R¹² is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -C(O)R^v, -C(O)OR^w and -C(O)NR^yR^z, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one to four substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R¹³ and R¹⁴ are selected as follows:

(i) R¹³ is hydrogen or alkyl; and R¹⁴ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy, -C(O)R^v, -C(O)OR^w, -C(O)NR^yR^z and -S(O)_qR^v, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally

substituted with one to four substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio; or

(ii) R¹³ and R¹⁴, together with the nitrogen atom to which they are attached, form heterocycll or heteroaryl wherein the heterocycll or heteroaryl are substituted with one to four substituents independently selected from halo, alkyl, hydroxy, alkoxy, amino and alkylthio and wherein the heterocycll is optionally substituted with oxo;

R¹⁵ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycll, heterocycllalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -C(O)NR^yR^z or -NR^yR^z, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycll, heterocycllalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl are each optionally substituted with one to four substituents independently selected from halo, oxo, alkyl, hydroxy, alkoxy, amino and alkylthio;

R¹⁸ is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycll, heterocycllalkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl; wherein R¹⁸ is optionally substituted with 1 to 3 groups Q¹, each Q¹ independently selected from alkyl, hydroxyl, halo, oxo, haloalkyl, alkoxy, aryloxy, alkoxyalkyl, alkoxy carbonyl, alkoxy sulfonyl, carboxyl, cycloalkyl, heterocycll, aryl, heteroaryl, haloaryl and amino;

R¹⁹ and R²⁰ are selected as follows:

(i) R¹⁹ and R²⁰ are each independently hydrogen or alkyl; or
(ii) R¹⁹ and R²⁰, together with the nitrogen atom to which they are attached, form a heterocycll or heteroaryl which is optionally substituted with 1 to 2 groups each independently selected from halo, oxo, alkyl, haloalkyl, hydroxyl and alkoxy;

R²¹ is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl;
each R²² is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl or cycloalkyl; or both R²², together with the nitrogen atom to which they are attached, form a heterocycll optionally substituted with oxo;

R²³ is alkyl, alkenyl, alkynyl or haloalkyl;

R²⁴ is hydrogen or alkyl;

each R^x is independently alkylene, alkenylene, alkynylene or a direct bond;

R^Y is hydrogen, alkyl, alkenyl or alkynyl;

R^W is independently hydrogen, alkyl, alkenyl, alkynyl or haloalkyl;

R^Y and R^Z are selected as follows:

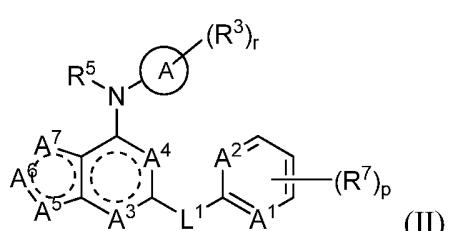
- (i) R^Y and R^Z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl or heterocyclyl;
- (ii) R^Y and R^Z , together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl which are optionally substituted with 1 to 2 groups each independently selected from halo, alkyl, haloalkyl, hydroxyl and alkoxy;

r is 1-3;

p is 0-4; and

each q is independently 0, 1 or 2.

2. The compound of claim 1, wherein the compound is of formula (II):



or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein

A is azolyl;

A^1 and A^2 are selected from N and CR^{7a} ; and

R^{7a} is hydrogen, alkyl

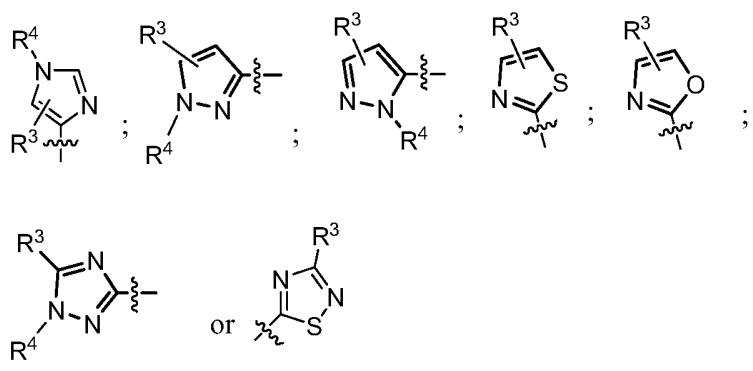
3. The compound of claims 1 or 2, wherein

L^1 is $-C(R^1)(R^2)-$, $-S(O)-$ or $-S(O)_2-$;

R^1 and R^2 are selected as follows:

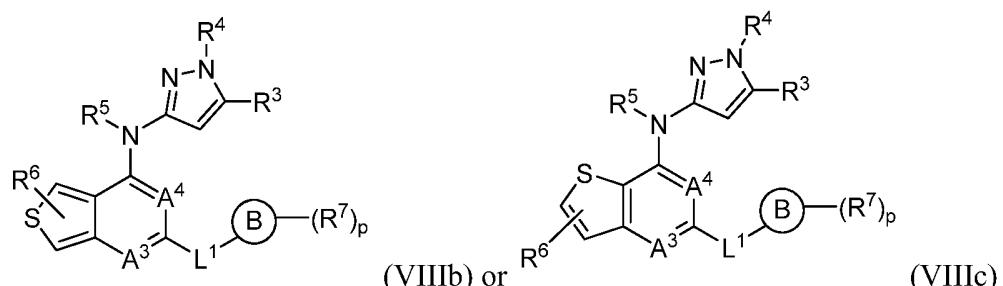
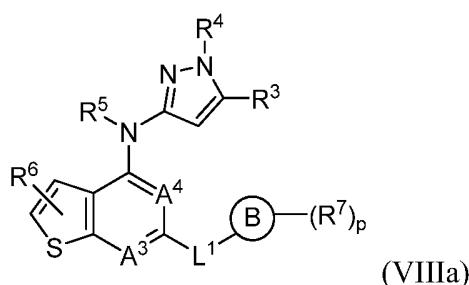
- (i) R^1 and R^2 together form $=O$;
- (ii) R^1 is hydrogen or halo; and R^2 is halo;
- (iii) R^1 is alkyl, and R^2 is hydrogen, alkyl, halo, hydroxyl or alkoxy; or
- (iv) R^1 is halo, hydroxyl or alkoxy; and R^2 is hydrogen or alkyl;

4. The compound of any of claims 1-3, wherein A is



wherein each R³ is independently hydrogen, deutoero, halo, alkyl, cyano, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxy or alkoxy; and each R⁴ is independently hydrogen, or alkyl.

5. The compound of any of claims 1-4, wherein R³ is hydrogen or alkyl.
6. The compound of any of claims 1-5, wherein each R⁶ is independently hydrogen, deutoero, cyano, halo, alkyl, alkoxy, haloalkoxy or cycloalkyl.
7. The compound of any of claims 1-5, wherein each R^{6s} is hydrogen.
8. The compound of any of claims 1-7, wherein R⁷ is halo.
9. The compound of claim 1 having formula (VIIIa), (VIIIb) or (VIIIc):



or a pharmaceutically acceptable salt, solvate or hydrate thereof, where R⁴ is hydrogen or alkyl.

10. The compound of claim 9, wherein

B is phenyl, pyridinyl or pyrimidinyl;

A³ and A⁴ are selected from N and CH, such that at least one of A³ or A⁴ is N;

L¹ is -C(R¹)(R²)-, -S(O)- or -S(O)₂-;

R¹ and R² are selected from (i), (ii), (iii) and (iv) as follows:

(i) R¹ and R² together form =O;

(ii) R¹ is hydrogen or halo; and R² is halo;

(iii) R¹ is alkyl, and R² is hydrogen, alkyl, halo, hydroxy or alkoxy;

and

(iv) R¹ is halo, hydroxy or alkoxy; and R² is hydrogen or alkyl;

R³ is hydrogen, alkyl or cycloalkyl,

R⁴ is hydrogen or alkyl;

R⁵ is hydrogen or alkyl;

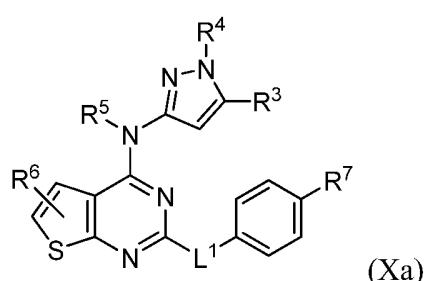
R⁶ is hydrogen, deutero, halo, cyano, alkyl, haloalkyl, alkoxy or haloalkoxy;

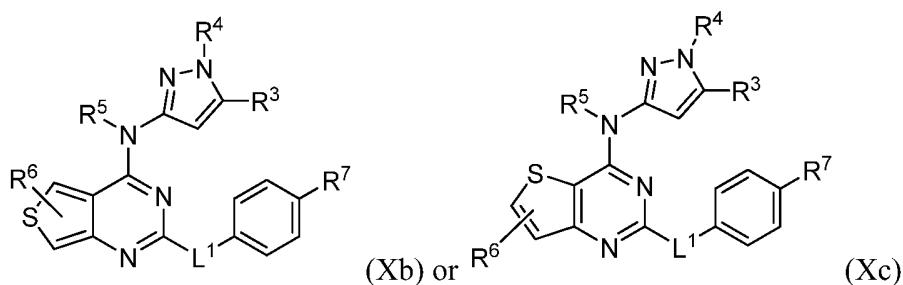
each R^{6a} is hydrogen or alkyl;

each R⁷ is independently halo, alkyl, haloalkyl or alkoxy; and

p is 0-2.

11. The compound of claim 1 having formula (Xa), (Xb) or (Xc)





or a pharmaceutically acceptable salt, solvate or hydrate thereof, where R^3 is hydrogen, alkyl or cycloalkyl; and R^4 is hydrogen or alkyl.

12. The compound of claim 11 having formula (Xa), (Xb) or (Xc) wherein L^1 is $-C(R^1)(R^2)-$, $-S(O)-$ or $-S(O)_2-$; R^1 and R^2 are selected from (i), (ii), (iii) and (iv) as follows:

- (i) R^1 and R^2 together form $=O$;
- (ii) R^1 is hydrogen or halo; and R^2 is halo;
- (iii) R^1 is alkyl, and R^2 is hydrogen, alkyl, halo, hydroxy or alkoxy;

and

- (iv) R^1 is halo, hydroxy or alkoxy; and R^2 is hydrogen or alkyl; R^3 is hydrogen, alkyl or cycloalkyl; R^5 is hydrogen or alkyl; R^4 is hydrogen or alkyl; R^6 hydrogen, halo, cyano, alkyl, or haloalkyl; and R^7 is halo.

13. The compound of claim 1 selected from:

- 2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine;
- 2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine;
- (4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanone;
- (4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanol;

(4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanone;

(4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanol;

2-(difluoro(4-fluorophenyl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine;

2-(difluoro(4-fluorophenyl)methyl)-N-(1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine;

2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine;

2-(difluoro(4-fluorophenyl)methyl)-6-methyl-N-(5-methyl-1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine;

2-(difluoro(4-fluorophenyl)methyl)-6-methyl-N-(1H-pyrazol-3-yl)thieno[2,3-d]pyrimidin-4-amine;

(4-fluorophenyl)(6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanol;

(4-fluorophenyl)(6-methyl-4-((1-methyl-1H-imidazol-4-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanol;

(4-((1H-pyrazol-3-yl)amino)-6-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanol;

(4-fluorophenyl)(6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanone;

(4-fluorophenyl)(7-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanone;

(4-fluorophenyl)(7-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanol;

(4-((1H-pyrazol-3-yl)amino)-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone;

(4-((1H-pyrazol-3-yl)amino)-7-methylthieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol;

(6-(tert-butyl)-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone;

(4-((1H-pyrazol-3-yl)amino)-6-(tert-butyl)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanone;
(4-fluorophenyl)(6-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)methanol;
(6-(tert-butyl)-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol;
(4-((1H-pyrazol-3-yl)amino)-6-(tert-butyl)thieno[3,2-d]pyrimidin-2-yl)(4-fluorophenyl)methanol;
2-(difluoro(4-fluorophenyl)methyl)-6-ethyl-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine compound with propane (1:1);
2-(difluoro(4-fluorophenyl)methyl)-6-ethyl-N-(1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine compound with propane (1:1);
(4-fluorophenyl)(5-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanone;
(4-((1H-pyrazol-3-yl)amino)-5-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanone;
(4-fluorophenyl)(5-methyl-4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[2,3-d]pyrimidin-2-yl)methanol;
(4-((1H-pyrazol-3-yl)amino)-5-methylthieno[2,3-d]pyrimidin-2-yl)(4-fluorophenyl)methanol;
1-(4-fluorophenyl)-1-(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,2-d]pyrimidin-2-yl)ethanol;
2-((4-fluorophenyl)(methoxy)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine;
(4-fluorophenyl)(4-((5-methyl-1H-pyrazol-3-yl)amino)thieno[3,4-d]pyrimidin-2-yl)methanol;
2-(4-fluorobenzyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine;
and
2-(difluoro(5-fluoropyridin-2-yl)methyl)-N-(5-methyl-1H-pyrazol-3-yl)thieno[3,2-d]pyrimidin-4-amine;
or a pharmaceutically acceptable salt, solvate or hydrate thereof.

14. A pharmaceutical composition comprising a compound of any of claims 1-13 and a pharmaceutically acceptable carrier, diluent or excipient.
15. A method for treatment of a JAK modulated disease comprising administering a therapeutically effective amount of a compound of any of claims 1-13.
16. A method for treatment of a JAK2 modulated disease comprising administering a therapeutically effective amount of a compound of any of claims 1-13.
17. The method of claim 16, wherein JAK2 is wild type or mutant JAK2.
18. The method of claim 17, wherein the disease is cancer, myeloproliferative disorder, inflammation or autoimmune disease.
19. The method of claim 18, further comprising administering a second pharmaceutical agent selected from anti-proliferative agent, anti-inflammatory agent, immunomodulatory agent and immunosuppressive agent.
20. The compound of any of claims 1-13 for treating a JAK modulated disease.
21. Use of the compound of any of claims 1-13 for preparation of a medicament for treating a JAK modulated disease.

INTERNATIONAL SEARCH REPORT

International application No PCT/US2011/049859

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D495/02 A61K31/4743 A61P35/00 A61P29/00 A61P37/00 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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

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

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/117995 A2 (TAKEDA SAN DIEGO INC [US]; DONG QING [US]; WALLACE MICHAEL B [US]) 18 October 2007 (2007-10-18) paragraph [0011] - paragraph [0031]; claims; examples 2, 8 -----	1-21
X	WO 2007/038519 A1 (WYETH CORP [US]; BOSCHELLI DIANE HARRIS [US]; COLE DEREK CECIL [US]; A) 5 April 2007 (2007-04-05) Formula (I); claims; examples -----	1-21
X	WO 2010/038060 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; CHUAQUI CLAUDIO EDMUNDO) 8 April 2010 (2010-04-08) Formula (I); claims; examples ----- -/-	1-21

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 2011	26/10/2011
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Kirsch, Cécile

INTERNATIONAL SEARCH REPORT

International application No PCT/US2011/049859

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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