ANILINOPYRIMIDINES AS JAK KINASE INHIBITORS

Provided herein are pyrimidine compounds, and methods of making and using the same. Such compounds may be used in inflammatory or myeloproliferative disorders. The disclosure also provides for treating cancer.
ANILINOPYRIMIDINES AS JAK KINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/977,826, filed October 5, 2007, and to U.S. Provisional Application No. 61/087,129, filed August 7, 2008, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] Protein kinases are enzymes that play key roles in signaling pathways since they catalyze the phosphorylation of specific residues leading to the transduction of extra and intra cellular signals, including the action of cytokines on their receptors, growth factors, communication with the nuclei and the triggering of various biological events. In normal cellular physiology, cell cycle control, cell growth, differentiation, apoptosis, mobility, mitogenesis, and various other structural and functional events appear to be mediated by kinases.

[0003] Aberrant kinase activity has been implicated in many diseases including cancers, in immunological and auto-immune disorders, in diabetes, fibrosis of the liver and kidney, atherosclerosis and in ocular diseases. Inhibition of such kinase activity may be beneficial in e.g., the treatment of such diseases.

[0004] The Janus kinases (JAKs) are cellular kinases and consist of four members - JAK1, JAK2, JAK3 and TYK2. The JAKs may play a crucial role in regulating cell behavior induced by a number of cytokines. As such, compounds which modulate the activity of the JAKs have potential utility in several indications driven by a dysregulation of signaling pathways normally associated with cytokine regulation. This includes immune and inflammatory diseases in which dysregulated cytokine pathways are thought to play a roles. In addition, somatic mutations in the hematopoietic system leading to activation of the JAK pathway has been linked to the myeloproliferative disorders, of cells proliferation and in several cells related to several kinds of immune function. Through the angiogenic role of JAK2 downstream of EPO receptors, JAK kinases have been implicated in ocular diseases such as
Age Related Macular Degeneration (AMD), diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).

[0005] Accordingly, there is a need to develop compounds useful as modulators of kinases, particularly, JAK kinase, given the inadequate treatments available for the aforementioned diseases where the JAK signaling pathway is dysregulated, or recruited directly or indirectly.

SUMMARY

[0006] Provided herein are novel compounds that may inhibit and/or modulate JAK, for example, JAK2. In some embodiments, the disclosed compounds may inhibit or modulate one or more of the JAK family, e.g., JAK1, JAK2, JAK3, and/or TYK2, and/or may inhibit or modulate KDR. Treatment or amelioration of disease states and pathological conditions that implicate JAK, e.g., JAK2, pathways are contemplated herein, and such treatment comprises administering one or more of the disclosed compounds, such as those recited in Formulas I, II, or III, or administering a composition as described herein comprising a disclosed compound. For example, disclosed compounds may have a IC_{50} against a JAK of less than about 500 nM.

[0007] Also contemplated herein are methods of treating myeloproliferative disorders such as polycythemia vera, myelofibrosis, and essential thrombocythemia by administering disclosed compounds. Additionally, methods of treating affliction such as cancer and/or inflammation are contemplated.

DETAILED DESCRIPTION

[0008] The present disclosure is directed in part towards novel compounds and compositions that modulate or inhibit JAK and methods of making and using the same.

[0009] In some embodiments, the disclosed compounds may inhibit or modulate one or more of the JAK family, e.g., JAK1, JAK2, JAK3, and/or TYK2, and/or may inhibit or modulate KDR.

[0010] Before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art.
Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

[0011] The term "therapeutic agent" is art-recognized and refers to any chemical moiety that is a biologically, physiologically, or pharmacologically active substance that acts locally or systemically in a subject. Examples of therapeutic agents, also referred to as "drugs", are described in well-known literature references such as the Merck Index, the Physicians Desk Reference, and The Pharmacological Basis of Therapeutics, and they include, without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of a disease or illness; substances which affect the structure or function of the body; or pro-drugs, which become biologically active or more active after they have been placed in a physiological environment.

[0012] The term "therapeutic effect" is art-recognized and refers to a local or systemic effect in animals, particularly mammals, and more particularly humans caused by a pharmacologically active substance. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and/or conditions in an animal or human. The phrase "therapeutically-effective amount" means that amount of such a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. The therapeutically effective amount of such substance will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. For example, certain compositions of the present invention may be administered in a sufficient amount to produce some desired local or systemic effect at a reasonable benefit/risk ratio applicable to such treatment.

[0013] The term "modulation" is art-recognized and refers to up regulation (i.e., activation or stimulation), down regulation (i.e., inhibition or suppression) of a response, or the two in combination or apart.

[0014] A "patient," "subject" or "host" to be treated by the subject method may mean either a human or non-human animal.
[0015] The term "treating" is art-recognized and refers to curing as well as ameliorating at least one symptom of any condition or disease.

[0016] The term "prodrug" is art-recognized and is intended to encompass compounds which, under physiological conditions, are converted into the agents of the present invention. A common method for making a prodrug is to select moieties which are hydrolyzed under physiological conditions to provide the desired compound. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal or the target organ or cell.

[0017] The term "alkyl" is art-recognized, and includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C₁₋C₃₀ for straight chain, C₃₋C₃₀ for branched chain), and alternatively, about 20 or fewer, e.g. from 1 to 6 carbons. Likewise, cycloalkyls have from about 3 to about 10 carbon atoms in their ring structure, and alternatively about 5, 6 or 7 carbons in the ring structure. The term "alkyl" is also defined to include halosubstituted alkyls.

[0018] Moreover, the term "alkyl" (or "lower alkyl") includes "substituted alkyls", which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents may include, for example, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfite, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain may themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CN and the like. Exemplary substituted alkyls are
described below. Cycloalkyls may be further substituted with alkyls, alkenyls, alkoxyys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CN, and the like.

[0019] The term "aralkyl" is art-recognized and refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

[0020] The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively. The term "alkylene" refers to an organic radical formed from an unsaturated aliphatic hydrocarbon; "alkenylene" denotes an acyclic carbon chain which includes a carbon-to-carbon double bond.

[0021] Unless the number of carbons is otherwise specified, "lower alkyl" refers to an alkyl group, as defined above, but having from one to about ten carbons, alternatively from one to about six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths.

[0022] The term "heteroatom" is art-recognized and refers to an atom of any element other than carbon or hydrogen. Illustrative heteroatoms include boron, nitrogen, oxygen, phosphorus, sulfur and selenium.

[0023] The term "aryl" as used herein refers to a mono-, bi-, or other multi-carbocyclic, aromatic ring system. The aromatic ring may be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, -CF₃, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, and/or aryls. Exemplary aryl groups include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl.
The terms ortho, meta and para are art-recognized and refer to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

The terms "heteroaryl" or "heteroaromatics" are art-recognized and refer to a 5-15 membered mono-, bi-, or other multi-cyclic, aromatic ring system containing one or more heteroatoms, for example one to four heteroatoms, such as nitrogen, oxygen, and sulfur. Heteroaryls can also be fused to non-aromatic rings. The heteroaryl ring may be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocycl, an aromatic or heteroaromatic moiety, -CF₃, -CN, or the like. Illustrative examples of heteroaryl groups include, but are not limited to, acridinyl, benzimidazolyl, benzofuranyl, benzothiazolyl, benzothienyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furazanyl, furyl, imidazolyl, indazolyl, indolizinyl, indolyl, isobenzofuranyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyrazinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyridazinyl, quinolinyl, quinolinyl, quinoline, quinoxalinyl, quinoxalyl, quinazolinyl, tetrazolyl, thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thiophenyl, triazinyl, (1,2,3)- and (1,2,4)-tri azolyl, and the like. Exemplary heteroaryl groups include, but are not limited to, a monocyclic aromatic ring, wherein the ring comprises 2 to 5 carbon atoms and 1 to 3 heteroatoms.

The terms "heterocycl" or "heterocyclic group" are art-recognized and refer to saturated or partially unsaturated 3- to 10-membered ring structures, alternatively 3- to 7-membered rings, whose ring structures include one to four heteroatoms, such as nitrogen, oxygen, and sulfur. Heterocycles may also be mono-, bi-, or other multi-cyclic ring systems. A heterocycle may be fused to one or more aryl, partially unsaturated, or saturated rings. Heterocyclic groups include, for example, biotinyl, chromenyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, homopiperidinyl, imidazolidinyl, isoquinolyl, isothiazolidinyl, isoaxazolidinyl, morpholinyl, oxolanyl, oxazolidinyl, phenoxanthenyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolidinyl,
pyrrolidin-2-onyl, pyrrolinyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydropyranyl,
tetrahydroquinolyl, thiazolidinyl, thiolanyl, thiomorpholinyl, thiopyranyl, xanthenyl, lactones,
lactams such as azetidinones and pyrrolidonones, sultams, sultones, and the like. The
heterocyclic ring may be substituted at one or more positions with such substituents as
described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl,
hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl,
carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or
heteroaromatic moiety, -CF₃, -CN, or the like.

[0027] The term "heterocycloalkyl" is art-recognized and refers to a saturated heterocyclyl
group as defined above.

[0028] The terms "polycyclyl" or "polycyclic group" are art-recognized and refer to two or
more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in
which two or more carbons are common to two adjoining rings, e.g., the rings are "fused
rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of
the rings of the polycycle may be substituted with such substituents as described above, as for
example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro,
sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio,
sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF₃, -
CN, or the like.

[0029] The term "carbocycle" is art-recognized and refers to an aromatic or non-aromatic
ring in which each atom of the ring is carbon.

[0030] The term "nitro" is art-recognized and refers to -NO₂; the term "halogen" is art-
recognized and refers to -F, -Cl, -Br or -I; the term "sulfhydryl" is art-recognized and refers to
-SH; the term "hydroxyl" means -OH; and the term "sulfonyl" is art-recognized and refers to -
SO₂.

[0031] The terms "amine" and "amino" are art-recognized and refer to both unsubstituted
and substituted amines, e.g., a moiety that may be represented by the general formulas:
wherein R50, R51 and R52 each independently represent a hydrogen, an alkyl, an alkenyl, -(CH2)m-R61, or R50 and R51, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R61 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In certain embodiments, only one of R50 or R51 may be a carbonyl, e.g., R50, R51 and the nitrogen together do not form an imide. In other embodiments, R50 and R51 (and optionally R52) each independently represent a hydrogen, an alkyl, an alkenyl, or -(CH2)m-R61. Thus, the term "alkylamine" includes an amine group, as defined above, having a substituted or unsubstituted alkyl attached thereto, i.e., at least one of R50 and R51 is an alkyl group.

[0032] The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that may be represented by the general formula:

wherein R50 and R51 are as defined above. Certain embodiments of the amide in the present invention will not include imides which may be unstable.

[0033] The term "acylamino" is art-recognized and refers to a moiety that may be represented by the general formula:
[0034] wherein R50 is as defined above, and R54 represents a hydrogen, an alkyl, an alkenyl or -(CH2)m-R61, where m and R61 are as defined above.

[0035] The term "alkythio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In certain embodiments, the "alkythio" moiety is represented by one of -S-alkyl, -S-alkenyl, -S-alkynyl, and -S-(CH2)m-R61, wherein m and R61 are defined above. Representative alkythio groups include methylthio, ethylthio, and the like.

[0036] The term "carbonyl" is art recognized and includes such moieties as may be represented by the general formulas:

\[
\begin{align*}
\text{O} & \quad \text{R55} \\
\text{X50} & \quad \text{R56}
\end{align*}
\]

wherein X50 is a bond or represents an oxygen or a sulfur, and R55 and R56 represents a hydrogen, an alkyl, an alkenyl, -(CH2)m-R61 or a pharmaceutically acceptable salt, R56 represents a hydrogen, an alkyl, an alkenyl or -(CH2)m-R61, where m and R61 are defined above. Where X50 is an oxygen and R55 or R56 is not hydrogen, the formula represents an "ester". Where X50 is an oxygen, and R55 is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R55 is a hydrogen, the formula represents a "carboxylic acid". Where X50 is an oxygen, and R56 is hydrogen, the formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X50 is a sulfur and R55 or R56 is not hydrogen, the formula represents a "thioester." Where X50 is a sulfur and R55 is hydrogen, the formula represents a "thiolcarboxylic acid." Where X50 is a sulfur and R56 is hydrogen, the formula represents a "thiolformate." On the other hand, where X50 is a bond, and R55 is
not hydrogen, the above formula represents a "ketone" group. Where X50 is a bond, and R55 is hydrogen, the above formula represents an "aldehyde" group.

[0037] The definition of each expression, e.g. alkyl, m, n, and the like, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

[0038] Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[0039] If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[0040] It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction.

[0041] The term "substituted" is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents
of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

[0042] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover. Also for purposes of this invention, the term "hydrocarbon" is contemplated to include all permissible compounds having at least one hydrogen and one carbon atom. In a broad aspect, the permissible hydrocarbons include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic organic compounds that may be substituted or unsubstituted.

[0043] The term "pharmaceutically-acceptable salts" is art-recognized and refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds, including, for example, those contained in compositions of the present invention.

[0044] The term "pharmaceutically acceptable carrier" is art-recognized and refers to a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition or component thereof from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the subject composition and its components and not injurious to the patient. Some examples of materials which may serve as pharmaceutically acceptable carriers include:

(1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol;
(12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[0045] The terms "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" are art-recognized and refer to the administration of a subject composition, therapeutic or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0046] The term "ocular administration" refers to the administration of a subject composition, therapeutic or other material on or into the eye, including topical and parenteral administration.

[0047] "Inhalation administration" or "administered by inhalation" refers to administration of a subject composition, therapeutic or other material by a pulmonary route, e.g. aerosol inhalation or nasal administration.

[0048] The terms "parenteral administration" and "administered parenterally" are art-recognized and refer to modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articular, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

Compounds

[0049] Contemplated herein, in part, are compounds of formula I:
In Formula 1, \( R_1 \) may be a heteroaryl optionally substituted on a ring carbon by one or two substituents each independently selected from the group consisting of halo, hydroxyl, nitro, formyl, cyano, formamido, carboxy, amino, amido, acylamino, carbamoyl, sulphanamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy-carbonyl, benzothiophene.

\( R_1 \) may contain at least one S atom. For example, \( R_1 \) can be selected from the group consisting of optionally substituted thiophene (thienyl) or optionally substituted benzo-thiophene.

\( R_2 \) may be a heterocycle, e.g. a phenyl or pyridinylop, wherein \( R_2 \) is optionally substituted on a ring carbon by one or two substituents each independently selected from the group consisting of halo, hydroxyl, nitro, formyl, formamido, cyano, carboxy, amino, amido, acylamino, CF, carbamoyl, sulphanamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy-carbonyl, N-alkylsulphanamoyl, N-alkyl-carbamoyl, -OR, -ORuR, -NR-R, or -R-R.

For example, \( R_1 \) may be, in some embodiments, an optionally substituted monocyclic or bicyclic heteroaryl. In some embodiments, alkyl may be chosen from methyl, ethyl, or propyl. \( R_1 \) may contain at least one S atom. For example, \( R_1 \) can be selected from the group consisting of optionally substituted thiophene (thienyl) or optionally substituted benzo-thiophene.

\( R' \) is alkyl optionally substituted with one, two or three halogens, for example, \( R' \) may be methyl; \( R_b \) is \( H \) or alkyl;

\( R_{11} \) is independently selected from aryl, heteroaryl, cycloalkyl and heterocycloalkyl, wherein \( R_{11} \) can be optionally substituted by one to four substituents each independently selected from with halo, alkyl, carbonyl, of halo, hydroxyl, nitro, formyl, formamido, cyano, carboxy, amino, amido, carbamoyl, sulphanamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy-carbonyl, N-alkylsulphanamoyl, N,N-dialkyl-sulphanamoyl, N-alkyl-carbamoyl, -O-alkylene-\( R_i \); or -SO_2-\( R_i \).

\( R_{12} \) is alkylene, sulfonyl, carbonyl, or a bond;

\( R_{4} \) is alkylene, alkenylene, sulfonyl, or a bond;

\( R_{3} \) is independently selected from aryl, heteroaryl, cycloalkyl and heterocycloalkyl, wherein \( R_{3} \) can be optionally substituted by one to four substituents each independently selected from with halo, alkyl, carbonyl, hydroxyl, nitro, formyl, formamido, carboxy, cyano,
amino, amido, carbamoyl, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkylsulphamoyl, N,N-dialkylsulphamoyl, N-alkyl carbamoyl.

[0057] Pharmaceutically acceptable salts, prodrugs, N-oxides, diastereomers, and/or hydrates of the compounds of Formula I are also contemplated herein.

[0058] In some embodiments, \( R_1 \) is represented by:

\[
\begin{align*}
\text{wherein } R_3 \text{ and } R_4 & \text{ may each be independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, formyl, formamido, carboxy, amino, carbamoyl, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkylsulphamoyl, N-alkyl carbamoyl,} \\
& \text{OR}_{11}, -\text{OR}_{11}R_{11}, -\text{NR}_{11}R_{11}, \text{ or } -\text{R}_{11}R_{11}, \text{ or } R_3 \text{ and } R_4 \text{ taken together with the carbon atoms to which they are attached form a 5 or 6 membered carbocyclic or heterocyclic ring, optionally substituted by one to two substituents each independently selected from with halo, alkyl, carbonyl, hydroxyl, nitro, formyl, formamido, carboxy, amino, carbamoyl, sulphamoyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkylsulphamoyl, N,N-dialkylsulphamoyl, N-alkyl carbamoyl. For example, } R_1 \text{ can be selected from:}
\end{align*}
\]

[0059] For each occurrence, \( R_5 \) is independently selected from hydrogen, halo, hydroxyl, nitro, formyl, formamido, carboxy, amino, amido, acylamino, cyano, carbamoyl, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkylsulphamoyl, N-alkyl carbamoyl, or \(-\text{R}_{14}R_{11}\) and \( R_5' \) is selected from the group consisting of H, alkyl, sulphonyl, and carbonyl.
[0059] In other embodiments, R_2 can be represented by

![Diagram]

wherein:

\(X\) is N or CR_8;

R_7 and R_8, independently for each occurrence, is chosen from H, heterocycle, heteroaryl, -O-alkylene-heterocycle or -O-heteroaryl, wherein said heterocycle or heteroaryl is optionally substituted with one to three substituents each independently selected from halo, alkyl, carbonyl, cyano, CF_3, hydroxyl, nitro, formyl, formamido, carboxy, amino, carbamoyl, sulphamoyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphamoyl, and N-alkyl carbamoyl. For example, R_7 may be a methyl-substituted heterocycle or heteraryl. In some embodiments, at least one R_8 is H.

[0060] In a particular embodiment, R_8 is H and R_7 is a heterocycle (for example a methyl substituted heterocycle), or -O-alkylene-heterocycle. Such heterocycles may include pyrrolidinyl, piperazinyl, piperidinyl, or morpholinyl. In an alternative embodiment, R_8 is H and R_7 is an optionally substituted imidazole.

[0061] For example, R_8 is H and R_7 is selected from the group consisting of: methylpiperazine, piperazine, N-(4-(2-methyl-1H-imidazol-1-yl), imidazole, or 2-pyrrolidin-2-yloxy.

[0062] In a particular embodiment, X is CR_8. When R_2 is phenyl, in some embodiments, meta and/or para substitution of the phenyl, with respect to the 2-position NH on the pyrimidine may be favorable for JAK2 modulation. In other embodiments, the phenyl may be substituted at one meta position, or at the para position.
In an embodiment, this disclosure contemplates compounds of Formula I, wherein when R’ is methyl, inhibits JAK2 with an IC\textsubscript{50} at least about ten times lower as compared to a compound represented by Formula I when R’ is H, and R\textsubscript{1}, R\textsubscript{2}, R\textsubscript{b}, R\textsubscript{n} and R\textsubscript{13} are as defined above. For example, without being limited by any theory, a 5-methyl substituent (e.g. R’ is methyl) on the pyrimidine ring of Formula I may, when interacting with JAK2, "sit" in the JAK2 pocket and may associate with an S-methyl group of a methionine. In some embodiments, the R\textsubscript{b} substituent, e.g. methyl, may act to make the pyrimidine portion of Formula I hydrophobic. For example: compound A, where R’ is H, has a IC\textsubscript{50} against JAK2 of 1360nM, and compound B, where R’ is methyl, has a IC\textsubscript{50} against JAK2 of 105nM:

![Chemical structures](image-url)

When R\textsubscript{1} is thiophene, with attachment to the pyrimidine at the 2-position, a methyl at the 3-position on the thiophene may result in a loss of JAK2 activity when R’ is methyl, e.g. compound C:

![Chemical structures](image-url)

Without being bound by any theory, if R\textsubscript{1} of Formula I is a 3-position methyl substituted thiophene, together with a 5-methyl substituted pyrimidine of the Formula I core, the conformation of the thiophene may result in loss of biological activity, such as JAK2 activity.
[0066] Also contemplated by this disclosure are compounds represented by formula II or formula III:

![Chemical Structures](image)

wherein:

- $R_3$ and $R_4$ may each be independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, formyl, formamido, carboxy, cyano, amino, amido, acylamido, carbamoyl, sulphanoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphamoyl, N-alkyl carbamoyl, -OR$_1$, -NR$_b$R$_{11}$, or -R$_{11}$;

- $R_9$ is independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, formyl, formamido, carboxy, amino, amido, acylamino, cyano, carbamoyl, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphamoyl, or N-alkyl carbamoyl;

- X is NR$_6$ or CR$_8$;

- $R_6$ is H or alkyl;

- $R_7$ and $R_8$ are each independently chosen from H, -R$_{12}$, or -OR$_{12}$ wherein at least one $R_8$ is H;

- $R_b$ is H or alkyl;
R₁ᵋ is independently selected from aryl, heteroaryl, cycloalkyl and heterocycloalkyl, wherein R₁ᵋ can be optionally substituted by one to four substituents each independently selected from with halo, alkyl, carbonyl, halo, hydroxyl, nitro, formyl, formamido, cyano, carboxy, amino, amido, acylamino, carbamoyl, sulphanoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphonamoyl, N-alkyl carbamoyl, -O-alkylene-Rᵋ₃, or -SO₂-Rᵋ₃;

R₁₄ is independently selected from aryl, cycloalkyl, heteroaryl or heterocycloalkyl, each optionally substituted by one to four substituents each independently selected from with halo, alkyl, carbonyl, hydroxyl, nitro, formyl, formamido, carboxy, cyano, amino, amido, acylamino, carbamoyl, sulphanoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphonamoyl, or N-alkyl carbamoyl,

Rᵋ₂ is chosen from: alkylene or a bond;

Rᵋ₁₄ is chosen from: alkylene, alkenylene, -SO₂-, or a bond; or pharmaceutically acceptable salts, prodrugs, N-oxides, distereomers and/or hydrates thereof.

[0067] In some embodiments, at least one of R₇ and R₈ of Formula II or III is H. In others embodiments, R₃ is H. In other embodiments, R₄ is selected from the group consisting of: H, halo, cyano, carboxyl, alkyl, heteroaryl optionally substituted with 1, 2, or 3 substituents each independently selected from halo, alkyl or branched alkyl, -NH-phenyl or -phenyl, wherein said phenyl is optionally substituted with N-alkyl sulphonamoyl, heterocycle, -S(O)₂-heterocycle, straight chain alkyl, branched alkyl, or -O-alkylene-heterocycle.

[0068] R₉ may be, for example, selected from H or alkyl. For example, at least one R₉ may be an alkyl, such as methyl. In another embodiment, R₉ can be H.

[0069] In some embodiments, R₇ or R₈ is selected from the group consisting of:
In other embodiments, $R_3$ is H and $R_4$ is selected from the group consisting of:
Exemplary compounds of this disclosure include: (5-Methyl-4-thiophen-2-yl-pyrimidin-2-yl)-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; (5-Methyl-4-thiophen-2-yl-pyrimidin-2-yl)-phenyl-amine; (5-Methyl-4-thiophen-2-yl-pyrimidin-2-yl)-pyridin-3-yl-amine; [5-Methyl-4-(5-phenyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(4-methyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(5-methyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(3-methyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(3-methyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(5-chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-(5-(2,4-Dimethyl-thiazol-5-yl)-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-(5-(3-Isopropyl-phenoxy)-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; 5-{5-Methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid; 5-{5-Methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl-methanol; N-Methyl-3-{5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl}-benzenesulfonamide; N-fer?-Butyl-3-{5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl}
benzenesulfonamide; (5-Methyl-4-[5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-thiophen-2-yl]-pyrimidin-2-yl)-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine ; 5-{ 5-Methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophene-2-carbonitrile; 4-[5-(3,5-Dimethyl-isoxazol-4-yl)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; 5-Methyl-4-[5-(3-morpholin-4-yl-phenyl)-thiophen-2-yl]-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(imidazol-1-yl-phenyl) -amine; 4-[5-(3-Isopropyl-phenyl)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl]-(4-morpholin-4-yl-phenyl)-amine; (4-Imidazol-1-yl-phenyl)-{4-[5-(3-isopropyl-phenyl)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl] -amine; (5-Methyl-4-[5-[3-(morpholine-4-sulfonyl)-phenyl]-pyrimidin-2-yl]-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(5-phenylamino-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; 5-Methyl-4-[5-(3-piperazin-1-yl-phenyl)-thiophen-2-yl]-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-(5-Isoxazol-4-yl-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-[5-(1-Isobutyl-1H-pyrazol-4-yl)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-[5-(3-fert-Butyl-phenylamino)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; N-tert-Butyl-3-[5- {5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino] -pyrimidin-4-yl }] -thiophen-2-ylamino)-benzenesulfonamide; 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine; N-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenyl)-4-(benzo[b]thiophen-2-yl)-5-methylpyrimidin-2-amine; 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(4-(piperidin-4-yl)oxy)phenyl)pyrimidin-2-amine; 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(3-(piperazin-1-yl)phenyl)pyrimidin-2-amine; 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(6-(piperazin-1-yl)pyridin-3-yl)pyrimidin-2-amine; 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(4-(2-methyl-1H-imidazol-1-yl)phenyl) pyrimidin-2-amine; 5-Methyl-4-(5-methylbenzo[b]thiophen-2-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine; N-(4-(2-Pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-4-(5-methylbenzo[b]thiophen-2-yl)pyrimidin-2-amine; 2-(2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-yl)benzo[b]thiophene-6-carbonitrile; 2-(2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-yl)benzo[b]thiophene-7-carbonitrile; 2-(2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-yl)benzo[b]thiophene-4-carbonitrile; 5-{5-Methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; 5-Methyl-4-[5-(3-tert-Butyl-3-(5-{

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phenylamino]-pyrimidin-4-yl]thienylmethylene)-thiazolidine-2,4-dione; N-te/t-butyl-3-(5-(5-methyl-2-(4-(piperidin-1-ylmethyl)phenylamino)pyrimidin-4-yl)thiophen-2-y)benzenesulfonamide; 4-(5-(3,5-diethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3,5-dimethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(3-(morpholinomethyl)phenyl)pyrimidin-2-amine; N-tert-butyl-4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophen-2-yl)-5-methyl-N-(4-(2-pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 2-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)benzo[b]thiophene-4-carbonitrile; N-tert-butyl-3-(5-(5-methyl-2-(4-(piperidin-1-ylmethyl)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzenesulfonamide; 4-(5-(3,5-diethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(2-pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3,5-dimethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(piperidin-1-ylmethyl)phenyl)pyrimidin-2-amine; N-tert-butyl-3-(5-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzenesulfonamide; 4-(5-(3,5-diethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(2-pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3,5-dimethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(morpholinomethyl)phenyl)pyrimidin-2-amine; 4-(5-(2,6-dimethylphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(2,6-dimethoxyphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(2-isopropoxy-6-methoxyphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(2-isopropylphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(2-isopropylphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; N-isopropyl-4-(3-(5-methyl-2-(4-(2-pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzenesulfonamide; N,N-diethyl-3-(5-(5-methyl-2-(4-(2-pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzenesulfonamide; 4-(5-(3-isopropylphenyl)thiophen-2-yl)-5-methyl-N-(4-(morpholinomethyl)phenyl)pyrimidin-2-amine; (3-methyl-5-(5-methyl-2-(4-(2-pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)methanol; 4-(5-(3,5-dimethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(morpholinomethyl)phenyl)pyrimidin-2-amine; 4-(5-(3-
isopropylphenyl)thiophen-2-yl)-5-methyl-N-(4-(piperidin-1-ylmethyl)phenyl)pyrimidin-2-amine; 4-(5-(3-isopropoxyphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3-isopropylphenyl)thiophen-2-yl)-5-methyl-N-(4-((2-methyl-1H-imidazol-1-yl)methyl)phenyl)pyrimidin-2-amine; N-cyclopropyl-3-(5-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzenesulfonamide; 4-(5-(3-tert-butyl-5-methylphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3-isopropylphenyl)thiophen-2-yl)-5-methyl-N-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)pyrimidin-2-amine; 4-(5-(2-isopropoxyphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(2,3-dimethylphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(2,3-dimethoxyphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; N-methoxy-N-methyl-3-(5-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzamide; (3-(5-(5-methyl-2-(4-(2-pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)phenyl)(4-methylpiperazin-1-yl)methanone; N-tert-butyl-3-(5-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzamide; 5-methyl-4-(4-phenylthiophen-2-yl)-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(4-(3,5-dimethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3,5-dimethyl-1H-pyrazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 5-methyl-4-(5-(methylsulfonyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3,5-dimethylisoxazol-4-yl)benzo[b]thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 2,2-dimethyl-1-(2-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one; 1-(2-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)benzo[b]thiophen-5-yl)pentan-1-one; 4-
(5-(5-tert-butyl-1,2,4-oxadiazol-3-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(5-butyl-5-(morpholinomethyl)-2,5-dihydro-1,2,4-oxadiazol-3-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(5-tert-butyl-5-butyl-2,5-dihydro-1,2,4-oxadiazol-3-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(5-tert-butyl-1,2,4-oxadiazol-3-yl)benzo[b]thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(5-isopropyl-1,2,4-oxadiazol-3-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3,5-dimethyl-1H-pyrazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-((2-methyl-1H-imidazol-1-yl)methyl)phenyl)pyrimidin-2-amine; (2-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)benzo[b]thiophen-5-yl)(morpholino)methanone; 4-(5-(3,5-dimethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(3-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine; 3-methyl-5-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)thiophene-2-carbonitrile; 3-methyl-5-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)thiophene-2-carbonitrile; (2-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)benzo[b]thiophen-5-yl)(morpholino)methanone; 5-methyl-N-(3-(4-methylpiperazin-1-yl)phenyl)-4-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)pyrimidin-2-amine; N,N-diethyl-2-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide; 5-methyl-N-(3-(4-methylpiperazin-1-yl)phenyl)-4-(5-(methylsulfonyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)pyrimidin-2-amine; 1-(2-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone; 2-methyl-1-(2-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-l-one; (2-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)(morpholino)methanone; N-tert-butyl-2-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide; and (2-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)benzo[b]thiophen-5-yl)(piperidin-1-yl)methanone and pharmaceutically acceptable salts, hydrates, prodrugs, diastereomers, and/or N-oxides thereof.

[0072] Contemplated herein also compositions that include the disclosed compounds and a pharmaceutically acceptable carrier.
Dosages

[0073] The dosage of any compositions of the present invention will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration, and the form of the subject composition. Any of the subject formulations may be administered in a single dose or in divided doses. Dosages for the compositions of the present invention may be readily determined by techniques known to those of skill in the art or as taught herein.

[0074] In certain embodiments, the dosage of the subject compounds will generally be in the range of about 0.01 ng to about 10 g per kg body weight, specifically in the range of about 1 ng to about 0.1 g per kg, and more specifically in the range of about 100 ng to about 10 mg per kg.

[0075] An effective dose or amount, and any possible affects on the timing of administration of the formulation, may need to be identified for any particular composition of the present invention. This may be accomplished by routine experiment as described herein, using one or more groups of animals (preferably at least 5 animals per group), or in human trials if appropriate. The effectiveness of any subject composition and method of treatment or prevention may be assessed by administering the composition and assessing the effect of the administration by measuring one or more applicable indices, and comparing the post-treatment values of these indices to the values of the same indices prior to treatment.

[0076] The precise time of administration and amount of any particular subject composition that will yield the most effective treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a subject composition, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage and type of medication), route of administration, and the like. The guidelines presented herein may be used to optimize the treatment, e.g., determining the optimum time and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the subject and adjusting the dosage and/or timing.
While the subject is being treated, the health of the patient may be monitored by measuring one or more of the relevant indices at predetermined times during the treatment period. Treatment, including composition, amounts, times of administration and formulation, may be optimized according to the results of such monitoring. The patient may be periodically reevaluated to determine the extent of improvement by measuring the same parameters. Adjustments to the amount(s) of subject composition administered and possibly to the time of administration may be made based on these reevaluations.

Treatment may be initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage may be increased by small increments until the optimum therapeutic effect is attained.

The use of the subject compositions may reduce the required dosage for any individual agent contained in the compositions because the onset and duration of effect of the different agents may be complimentary.

Toxicity and therapeutic efficacy of subject compositions may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 and the ED50.

The data obtained from the cell culture assays and animal studies may be used in formulating a range of dosage for use in humans. The dosage of any subject composition lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For compositions of the present invention, the therapeutically effective dose may be estimated initially from cell culture assays.

Formulations

The compositions of the present invention may be administered by various means, depending on their intended use, as is well known in the art. For example, if compositions of the present invention are to be administered orally, they may be formulated as tablets, capsules, granules, powders or syrups. Alternatively, formulations of the present invention may be administered parenterally as injections (intravenous, intramuscular or subcutaneous),
drop infusion preparations, suppositories or administration intranasally (for example, to deliver a dosage to the brain via the nose or to deliver a dosage to the nose directly) or by inhalation (e.g. to treat a condition of the respiratory tract or to pretreat or vaccinate via the respiratory tract). For application by the ophthalmic mucous membrane route, compositions of the present invention may be formulated as eyedrops or eye ointments. These formulations may be prepared by conventional means, and, if desired, the compositions may be mixed with any conventional additive, such as an excipient, a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent or a coating agent.

[0083] In formulations of the subject invention, wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants may be present in the formulated agents.

[0084] Subject compositions may be suitable for oral, nasal, topical (including buccal, ocular, and sublingual), rectal, vaginal, aerosol, ocular, and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of composition that may be combined with a carrier material to produce a single dose vary depending upon the subject being treated, and the particular mode of administration.

[0085] Methods of preparing these formulations include the step of bringing into association compositions of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association agents with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0086] Formulations suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia), each containing a predetermined amount of a subject composition thereof as an active ingredient. Compositions of the present invention may also be administered as a bolus, electuary, or paste.
In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

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

[0090] Suspensions, in addition to the subject composition, may contain suspending agents as,
for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters,
microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and
mixtures thereof.

[0091] Formulations for rectal or vaginal administration may be presented as a suppository,
which may be prepared by mixing a subject composition with one or more suitable non-
irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a
suppository wax or a salicylate, and which is solid at room temperature, but liquid at body
temperature and, therefore, will melt in the body cavity and release the active agent.
Formulations which are suitable for vaginal administration also include pessaries, tampons,
creams, gels, pastes, foams or spray formulations containing such carriers as are known in the
art to be appropriate.

[0092] Dosage forms for transdermal administration of a subject composition includes
powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The
active component may be mixed under sterile conditions with a pharmaceutically acceptable
carrier, and with any preservatives, buffers, or propellants which may be required.

[0093] The ointments, pastes, creams and gels may contain, in addition to a subject
composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch,
tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc
and zinc oxide, or mixtures thereof.

[0094] Powders and sprays may contain, in addition to a subject composition, excipients such
as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or
mixtures of these substances. Sprays may additionally contain customary propellants, such as
chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and
propane.
Compositions and compounds of the present invention may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions.

Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

Dosages for administration by nasal delivery, e.g. delivered to or via the nasal cavity, can be applied as drops, ointments, gels, mists/sprays (aqueous or nonaqueous), aerosols (liquids, suspensions or dry powders), powders, or combinations thereof. Such delivery can be achieved by commercially available devices such as droppers, nasal sprayers, metered dose aerosols, or other mechanisms known in the art. Pharmaceutical formulations for inhalation and/or delivery to the nose, may contain from 1% to 20% by weight of a penetrator enhancer (for example, surfactants, e.g. sugar esters, sugar ethers, carbohydrate esters) which may allow enhanced nose permeability of the active agent.

Dosages for administration by inhalation or by delivered to or via the lung, can be applied as mists/sprays (aqueous or nonaqueous), aerosols (liquids, suspensions or dry powders), liquids or suspensions (aqueous or nonaqueous), powders, or combinations thereof. Such delivery can be achieved by commercially available devices such as 1) nebulizers, 2) metered dose inhalers, 3) dry powder inhalers, 4) soft mist inhalers, or by instillation or insufflation, or other mechanisms and/or devices known in the art.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or
sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0100] For topical ocular administration compositions of this invention may take the form of solutions, gels, ointments, suspensions or solid inserts, formulated so that a unit dosage comprises a therapeutically effective amount of the active component or some multiple thereof in the case of a combination therapy.

[0101] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

Methods

[0102] Treatment or amelioration of disease states and pathological conditions that implicate JAK, e.g. JAK2, pathways are contemplated herein, and such treatment comprises administering one or more of the disclosed compounds, such as those recited in Formulas I, II, or III, or a composition as described herein comprising a disclosed compound. In some embodiments, the disclosed compounds may inhibit or modulate one or more of the JAK family, e.g. JAK1, JAK2, JAK3, and/or TYK2, and/or may inhibit or modulate KDR. In other embodiments, the disclosed compounds may for example inhibit JAK2 but may not substantially modulate JAK3 and/or KDR.

[0103] Methods of treating a patient in need thereof, e.g. suffering from a disease where inhibition of kinases are useful, for example, immunological and autoimmune disorders, inflammatory disease, diabetes, fibrosis of the liver and/or kidney, atherosclerosis, and ocular diseases are contemplated.
Because JAKs appear to play a crucial role in regulating cell behavior induced by a number of cytokines, treatment of indications driven by a dysregulation of signaling pathways normally associated with cytokine regulation may include compounds which modulate the activity of the JAKs, such as those recited in Formulas I, II or III is contemplated, such as the treatment of immune and inflammatory diseases, e.g. rheumatoid arthritis (RA), psoriatic arthritis, asthma, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, type I diabetes mellitus, myasthenia gravis, thyroiditis, myocarditis, psoriasis, immunoglobulin nephropathies, uveitis, iritis, scleritis, conjunctivitis, graft versus host disease and dermatitis. Particularly, methods of treating asthma and/or chronic obstructive pulmonary disease (COPD) is contemplated.

Somatic mutations in the hematopoietic system leading to activation of the JAK pathway has been linked to the myeloproliferative disorders polycythemia vera, essential thrombocythemia and myeloid metaplasia with myelofibrosis. Similarly, upregulation of the JAK pathway may contribute to the myeloproliferative disorders chronic myelogenous leukemia, chronic myelomocytic leukemia, thalassemia gravis, hypereosinophilic syndrome, and systemic mast cell disease. Specifically contemplated herein are methods for treating cancers, e.g. cancers are associated with activation of Janus kinases including acute myeloid leukemia, hepatocellular carcinoma, multiple myeloma, prostrate cancer, Hodgkin's lymphomas and T cell leukemia/lymphoma, wherein the method includes administrating a disclosed compounds.

The angiogenic role of JAK2 downstream of the EPO receptor has been implicated in ocular diseases such as Age Related Macular Degeneration (AMD), diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR), and treatment of one or more of these diseases is contemplated. In an embodiment, a method of treating an ocular or other disease is contemplated that includes administration of a disclosed compound that modulates JAK and in some embodiments, inhibits VEGF. may also be an advantage.

Also contemplated herein is a method for treating or ameliorating transplant rejection that includes administering an instantly disclosed compound.

In an embodiment, a method for treating or ameliorating rheumatoid arthritis that includes administering an instantly disclosed compound is contemplated.
[0109] Dysregulation in the hematopoietic stem cells of the myeloid compartment may lead to related myeloproliferative disorders (MPDs) including polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF), and to acute myeloid leukemia (AML). Underlying each of these myeloid diseases may be a cytokine-independent activation of molecular signaling pathways critical for the proliferation and aberrant survival of the cells associated with the disease's pathology. For example, a majority of PV, ET, and MF patients harbor an activating valine to phenylalanine point mutation at residue 617 in Janus kinase 2 (JAK2<sup>V617F</sup>) that known suggest is necessary and sufficient for myeloid expansion and the symptoms manifested by these diseases. Along with JAK2<sup>V617F</sup>, there are less prevalent tyrosine kinase mutations, all of which constitutively activate JAK2 in these 3 diseases such as JAK2<sup>T875N</sup>, exon 12 mutations in JAK2, and mutations in the upstream thrombopoietin receptor (MPL<sup>W515L/K</sup>). Without being bound by any theory, JAK2 activation leads to phosphorylation of signal transducer and activator of transcription (STAT) proteins, transcription factors that stimulate the cell's genetic machinery to induce proliferation and prevent apoptosis. Similarly, AML features ligand-independent activation of the JAK-STAT pathway in the majority of patients. Although there is no predominant known mutation that leads to activation of the JAK-STAT pathway in AML, approximately 30% of AML patients appear to have this activation mediated through mutations in the FMS-like receptor tyrosine kinase 3 (FLT3). Methods of treating a patient suffering from acute leukaemias, myeloid and lymphoid malignancies or myeloproliferative disorders such as polycythemia vera, myelofibrosis, and essential thrombocythemia are contemplated and may comprise administering an effective amount of a disclosed compound, such as those recited in Formulas I, II, or III or a composition comprising a disclosed compounds. In an embodiment, a method of treatment of AML, PV, ET and MT, for example, in patients with mutations in FLT3, comprising administering a disclosed compound, e.g. a compound of Formulas I, II, or III.

[0110] Treatment of other cancers is contemplated comprising administering an effective amount of a disclosed compound. The treatment of cancers can include, but are not limited to, an alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer, breast cancer, ovarian cancer, prostate cancer, leukemia (including acute myelogenous leukemia and chronic myelogenous leukemia), kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer or brain cancer.
[0111] Also contemplated herein are methods of treating ocular neovascularization, infantile haemangiomas; organ hypoxia, vascular hyperplasia, organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type 1 diabetes and complications from diabetes, inflammatory disease, acute pancreatitis, chronic pancreatitis, asthma, allergies, adult respiratory distress syndrome, cardiovascular disease, liver disease, other blood disorders, asthma, rhinitis, atopic, dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, conditions associated with cytokines, and other autoimmune diseases including glomerulonephritis, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopy (e.g., allergic asthma, atopic dermatitis, or allergic rhinitis), chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, graft vs host disease, neurodegenerative diseases including motor neuron disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia, or neurodegenerative disease caused by traumatic injury, stroke, glutamate neurotoxicity or hypoxia; ischemic/reperfusion injury in stroke, myocardial ischemia, renal ischemia, heart attacks, cardiac hypertrophy, atherosclerosis and arteriosclerosis, organ hypoxia, and platelet aggregation. Such treatment includes administering an effective amount of a disclosed compound.

[0112] Examples of some additional diseases and disorders that can be treated using a disclosed include cell mediated hypersensitivity (allergic contact dermatitis, hypersensitivity pneumonitis), rheumatic diseases (e.g., systemic lupus erythematosus (SLE), juvenile arthritis, Sjogren's Syndrome, scleroderma, polymyositis, ankylosing spondylitis, psoriatic arthritis), viral diseases (Epstein Barr Virus, Hepatitis B, Hepatitis C, HIV, HTLVl, Vaicella-Zoster Virus, Human Papilloma Virus), food allergy, cutaneous inflammation, and immune suppression induced by solid tumors.

[0113] One embodiment provides for a process for forming a compound of Formula I comprising reacting a compound of formula IV:

\[
\begin{align*}
R & \quad \text{N} \\
R_1 & \quad \text{Y} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]
wherein $Y$ is a boronic acid or halogen, with $R_2\text{-NH}_2$ to obtain the compound of Formula I.

[0114] Another embodiment provides for a process for forming a compound of Formula II comprising reacting a compound of Formula V:

\[
\begin{array}{c}
\text{V} \\
R_3 \quad R_4 \\
\text{S} \\
\text{N} \\
\text{Y} \\
\end{array}
\]

wherein $Y$ is a boronic acid or halogen, with a compound of Formula VI:

\[
\begin{array}{c}
\text{VI} \\
\text{R}_7 \\
\text{X} \\
\text{H}_2\text{N} \\
\text{R}_3 \\
\end{array}
\]

to obtain the compound of Formula II.

[0115] Another embodiment provides for a process for forming a compound of Formula III comprising reacting a compound of Formula VII:

\[
\begin{array}{c}
\text{VII} \\
\text{R}_9 \\
\text{R}_9 \\
\text{S} \\
\text{N} \\
\text{Y} \\
\end{array}
\]

wherein $Y$ is a boronic acid or halogen, with a compound of Formula VI:
to obtain the compound of Formula III.

[0116] An exemplary synthetic procedure is depicted below:

[Suzuki coupling of starting materials A and B provides chloropyrimidine C, a compound of Formula IV. Reaction of C with aniline D, a compound of Formula R₂-NH₂, affords chlorothiophene E. Treatment of E with boronic acid F provides compound 81, a compound of Formula I.

[0117] The examples which follow are intended in no way to limit the scope of this invention but are provided to illustrate how to prepare and use compounds of the present invention. Many other embodiments of this invention will be apparent to one skilled in the art.
EXAMPLES

General Methods

[0119] All experiments were performed under anhydrous conditions (i.e. dry solvents) in an atmosphere of argon, except where stated, using oven-dried apparatus and employing standard techniques in handling air-sensitive materials. Aqueous solutions of sodium bicarbonate (NaHCO₃) and sodium chloride (brine) were saturated. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F₂₅₄ plates with visualization by ultraviolet and/or anisaldehyde, potassium permanganate or phosphomolybdic acid dips. Reverse-phase HPLC chromatography was carried out on Gilson 215 liquid handler equipped with Waters SymmetryShield™ RP18 7µm (40 x 100mm) Prep-Pak cartridge. Mobile phase consisted of standard acetonitrile (ACN) and DI Water, each with 0.1% TFA added. Purification was carried out at a flow rate of 40mL/min. NMR spectra: ¹H Nuclear magnetic resonance spectra were recorded at 500 MHz. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd = doublet of doublets, m = multiplet, br s = broad singlet), coupling constant (J/Hz) and integration. Coupling constants were taken directly from the spectra and are uncorrected. Low resolution mass spectra: Electrospray (ES+) ionization was used. The protonated parent ion (M+H) or fragment of highest mass is quoted. Analytical gradient consisted of 10% ACN in water ramping up to 100% ACN over 5 min unless otherwise stated.

[0120] EXAMPLE 1 Preparation of 2-Chloro-5-methyl-4-thiophen-2-yl-pyrimidine (1)

\[
\begin{array}{c}
\text{\includegraphics[width=1cm]{example1.png}} \\
\end{array}
\]

[0121] To a microwave reaction tube was charged with 2,4-dichloro-5-methyl-pyrimidine (0.50 g, 3.1 mmol), thiophene-2-boronic acid (0.45 g, 3.5 mmol) and Pd(PPh₃)₄ (0.20 g, 0.17 mmol). DMF (6 mL) was added to the above mixture followed by aqueous sodium carbonate
(2 M; 3.0 mL, 0.6 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 120 °C for 15 min. After cooling to room temperature, the mixture was filtered, the filtered solid washed with DCM and the filtrate concentrated. The crude product was purified by column chromatography on silica gel (hexanes to 40% EtOAc/hexanes) to afford the title compound (0.41 g, 63%) as a white solid.

[0122] ¹H NMR (500 MHz, DMSO-d₆): δ 2.52 (s, 3H), 7.30 (dd, J = 5.0, 4.0 Hz, IH), 7.91 (dd, J = 3.9, 0.8 Hz, IH), 7.95 (dd, J = 5.3, 0.8 Hz, IH), 8.65 (s, IH); MS (ES+): m/z 221 (M+H)⁺

[0123] EXAMPLE 2 Preparation of (5-Methyl-4-thiophen-2-yl-pyrimidin-2-yl)-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine:

![Chemical Structure]

[0124] A suspension of 1 (0.10 g, 0.47 mmol), 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.10 g, 0.49 mmol), Pd₂(dba)₃ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.30 g, 0.92 mmol) in dioxane (4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue triturated in a mixture of hexanes and EtOAc (hexanes/EtOAc = 5/1, 24 mL). After filtration, the title compound was obtained as a yellow solid (82 mg, 45%). ¹H NMR (500 MHz, DMSO-d₆): δ 1.65-1.72 (m, 4H), 2.40 (s, 3H), 2.48-2.58 (m, 4H), 2.78 (t, J = 5.7 Hz, 2H), 4.03 (t, J = 6.0 Hz, 2H), 6.89 (d, J = 9.2 Hz, 2H), 7.26 (dd, J = 5.0, 3.9 Hz, IH), 7.70 (d, J = 9.0 Hz, 2H), 7.77 (dd, J = 3.9, 0.9 Hz, IH), 7.81 (dd, J = 5.0, 0.9 Hz, IH), 8.34 (s, IH), 9.32 (s, IH); MS (ES+): m/z 381 (M+H)⁺

[0125] EXAMPLE 3 Preparation of (5-Methyl-4-thiophen-2-yl-pyrimidin-2-yl)-phenyl-amine
[0126] A suspension of 1 (0.10 g, 0.47 mmol), aniline (0.05 mL, 0.55 mmol), Pd\(_2\)(dba)\(_3\) (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.30 g, 0.92 mmol) in dioxane (4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by column chromatography on silica gel (hexanes to 30% EtOAc/hexanes) to afford the title compound (50 mg, 39%) as a white solid.

[0127] \(^1\)H NMR (500 MHz, DMSOd\(_6\)): \(\delta\) 2.42 (s, 3H), 6.93 (t, \(J = 7.3\) Hz, IH), 7.25-7.32 (m, 3H), 7.79 (dd, \(J = 3.9, 0.9\) Hz, IH), 7.80-7.85 (m, 3H), 8.40 (s, IH), 9.51 (s, IH); MS (ES\(^+\)): \(m/\ell 268\) (M+H)

[0128] EXAMPLE 4: Preparation of (5-Methyl-4-thiophen-2-yl-pyrimidin-2-yl)-pyridin-3-yl-amine

[0129] A suspension of 1 (0.10 g, 0.47 mmol), pyridin-3-ylamine (60 mg, 0.64 mmol), Pd\(_2\)(dba)\(_3\) (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.30 g, 0.92 mmol) in dioxane (4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO\(_3\) solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the
combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue triturated in a mixture of hexanes/EtOAc (5/1, 24 mL). After filtration, the title compound was obtained as a light brown solid (30 mg, 24%).

¹H NMR (500 MHz, DMSOd₆):  δ 2.44 (s, 3H), 7.28 (dd, J = 5.2, 3.8 Hz, IH), 7.34 (dd, J = 8.3, 4.6 Hz, IH), 7.81 (dd, J = 3.6, 0.9 Hz, IH), 7.85 (dd, J = 5.0, 0.9 Hz, IH), 8.15 (br s, IH), 8.26-8.29 (m, IH), 8.44 (s, IH), 8.97 (br s, IH), 9.73 (s, IH). MS (ES+): m/z 269 (M+H)⁺

[0130] EXAMPLE 5: Preparation of 2-Chloro-5-methyl-4-(5-phenyl-thiophen-2-yl)-pyrimidine (2)

[0131] To a microwave reaction tube was charged with 2,4-dichloro-5-methyl-pyrimidine (0.30 g, 1.84 mmol), 5-phenylthiophene-2-boronic acid (0.45 g, 2.2 mmol) and Pd(PPh₃)₄ (0.15 g, 0.13 mmol). DMF (6 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 2.0 mL, 0.4 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 120 °C for 20 min. After cooling to room temperature, the mixture was filtered, the filtered solid washed with DCM and the filtrate concentrated. The crude product was purified by column chromatography on silica gel (hexanes to 20% EtOAc/hexanes) to afford the title compound (0.20 g, 38%) as a yellow solid. ¹H NMR (500 MHz, DMSOd₆): δ 2.55 (s, 3H), 7.38-7.43 (m, IH), 7.48 (t, J = 7.5 Hz, 2H), 7.71 (d, J = 4.0 Hz, IH), 7.82 (d, J = 7.1 Hz, 2H), 7.91 (d, J = 4.2 Hz, IH), 8.65 (s, IH) MS (ES+): m/z 287 (M+H)⁺

A suspension of 2 (70 mg, 0.24 mmol), 4-(2-pyrrolidin-yl-ethoxy)-phenylamine (65 mg, 0.32 mmol), Pd2(dba)3 (15 mg, 0.016 mmol), Xantphos (20 mg, 0.035 mmol) and cesium carbonate (0.16 g, 0.49 mmol) in dioxane (10 mL) was heated at 100 °C under argon atmosphere for 3 h. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with EtOAc. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO3 solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na2SO4 and filtered. The filtrate was concentrated and the residue triturated in MeOH. After filtration, the title compound was obtained as a yellow solid (30 mg, 27%). 1H NMR (500 MHz, DMSO-d6): δ 1.65-1.75 (m, 4H), 2.43 (s, 3H), 2.50-2.60 (m, 4H), 2.75-2.85 (m, 2H), 4.05 (t, J = 5.9 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 7.39 (t, J = 7.4 Hz, IH), 7.48 (t, J = 7.7 Hz, 2H), 7.64 (d, J = 4.0 Hz, IH), 7.72 (d, J = 9.0 Hz, 2H), 7.60-7.80 (m, 3H), 8.35 (s, IH), 9.33 (s, IH); MS (ES+): m/z 457 (M+H)+

EXAMPLE 7: Preparation of 2-Chloro-5-methyl-4-(4-methyl-thiophen-2-yl)-pyrimidine (3)

To a round bottomed flask was charged with 2,4-dichloro-5-methyl-pyrimidine (0.30 g, 1.84 mmol), 4-methylthiophene-2-boronic acid (0.35 g, 2.5 mmol) and Pd(PPh3)4 (0.15 g, 0.13 mmol). DMF (10 mL) was added to the above mixture followed by aqueous sodium carbonate
The reaction mixture was heated at 110 °C for 1.5 h. After cooling to room temperature, the mixture was filtered and the filtered solid washed with EtOAc. The filtrate was washed with water (2 x 40 mL) and brine. The organic layer was separated, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue triturated in MeOH. After filtration, the title compound was obtained as a yellow solid (0.24 g, 58%).

[0136] ^1H NMR (500 MHz, DMSO-d₆): δ 2.29 (s, 3H), 7.54 (s, 1H), 7.75 (s, 1H), 8.62 (s, 1H); MS (ES+): m/z 241 (M+H)^+

[0137] EXAMPLE 8 Preparation of [5-Methyl-4-(4-methyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine

[0138] A suspension of 3 (0.10 g, 0.42 mmol), 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.12 g, 0.58 mmol), Pd₂(dba)₃ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.35 g, 1.1 mmol) in dioxane (10 mL) was heated at reflux under argon atmosphere for 3 h. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with EtOAc. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a yellow solid (72 mg, 44%).

[0139] ^1H NMR (500 MHz, DMSO-d₆): δ 1.65-1.72 (m, 4H), 2.29 (s, 3H), 2.39 (s, 3H), 2.48-2.58 (m, 4H), 2.79 (t, J = 5.1 Hz, 2H), 4.03 (t, J = 5.9 Hz, 2H), 6.88 (d, J = 9.4 Hz, 2H), 7.39
(s, IH), 7.59 (s, IH), 7.69 (d, J = 9.0 Hz, 2H), 8.32 (s, IH), 9.28 (s, IH); MS (ES+): m/z 395 (M+H) +

[0140] EXAMPLE 9 Preparation of 2-Chloro-5-methyl-4-(5-methyl-thiophen-2-yl)-pyrimidine (4)

To a round bottomed flask was charged with 2,4-dichloro-5-methyl-pyrimidine (0.30 g, 1.84 mmol), 5-methylthiophene-2-boronic acid (0.35 g, 2.5 mmol) and Pd(PPh3)4 (0.15 g, 0.13 mmol). DMF (10 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 2.5 mL, 5.0 mmol). The reaction mixture was heated at 110 °C for 1.5 h. After cooling to room temperature, the mixture was filtered and the filtered solid washed with EtOAc. The filtrate was washed with water (2 x 40 mL) and brine. The organic layer was separated, dried over anhydrous Na2SO4 and filtered. The filtrate was concentrated and the residue triturated in MeOH. After filtration, the title compound was obtained as a light brown solid (0.40 g, 67%).

[0141] 1H NMR (500 MHz, DMSO-d6): δ 2.53 (s, 3H), 7.01 (d, J = 3.9 Hz, IH), 7.72 (d, J = 3.9 Hz, IH), 8.56 (s, IH); MS (ES+): m/z 241 (M+H) +

[0142] EXAMPLE 10: Preparation of [5-Methyl-4-(5-methyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine

[0143]
[0144] A suspension of 4 (0.10 g, 0.42 mmol), 4-(2-pyrrolidin-l-yl-ethoxy)-phenylamine dihydrochloride (0.16 g, 0.57 mmol), Pd\(_2\)(dba)\(_3\) (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.80 g, 2.5 mmol) in dioxane (10 mL) was heated at reflux under argon atmosphere for 1 d. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO\(_3\) solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na\(_2\)SO\(_4\) and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (1/5, 30 mL). After filtration, the title compound was obtained as a light brown solid (30 mg, 18%).

[0145] \(^1\)H NMR (500 MHz, DMSO-d\(_6\)): 6 1.65-1.72 (m, 4H), 2.36 (s, 3H), 2.52 (s, 3H), 2.55-2.75 (m, 4H), 2.80-2.90 (m, 2H), 4.06 (t, J = 5.7 Hz, 2H), 6.90 (d, J = 9.1 Hz, 2H), 6.95 (dd, J = 3.8, 1.0 Hz, IH), 7.56 (d, J = 3.8 Hz, IH), 7.69 (d, J = 9.1 Hz, 2H), 8.29 (s, IH), 9.26 (s, IH); MS (ES+): m/z 395 (M+H)+

[0146] EXAMPLE 11 Preparation of 2-Chloro-5-methyl-4-(3-methyl-thiophen-2-yl)-pyrimidin (5)

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\begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{S} \\
\end{array}
\]

[0147] To a round bottomed flask was charged with 2,4-dichloro-5-methyl-pyrimidine (0.30 g, 1.84 mmol), 3-methylthiophene-2-boronic acid (0.35 g, 2.5 mmol) and Pd(PPh\(_3\))\(_4\) (0.15 g, 0.13 mmol). DMF (10 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 2.5 mL, 5.0 mmol). The reaction mixture was heated at 110 °C for 1.5 h. After cooling to room temperature, the mixture was filtered and the filtered solid washed with EtOAc. The filtrate was washed with water (2 x 40 mL) and brine. The organic layer was separated, dried over anhydrous Na\(_2\)SO\(_4\) and filtered. The filtrate was concentrated and the residue purified by column chromatography on silica gel (hexanes to 20% EtOAc/hexanes) to afford the title compound as a light brown oil (0.33 g, 74%). MS (ES+): m/z 241 (M+H)+
EXAMPLE 12: Preparation of [5-Methyl-4-(3-methyl-thiophen-2-yl)-pyrimidin-2-yl]-
[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine

A suspension of 5 (0.10 g, 0.42 mmol), 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.12 g, 0.58 mmol), Pd$_2$(dba)$_3$ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.35 g, 1.1 mmol) in dioxane (10 mL) was heated at reflux under argon atmosphere for 1 d. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO$_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na$_2$SO$_4$ and filtered. The filtrate was concentrated and dried under high vacuum to afford the title compound as a brown solid (80 mg, 49%).

$^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 1.65-1.72 (m, 4H), 2.10 (s, 3H), 2.18 (s, 3H), 2.50-2.58 (m, 4H), 2.78 (t, $J = 5.8$ Hz, 2H), 4.01 (t, $J = 6.0$ Hz, 2H), 6.85 (d, $J = 9.1$ Hz, 2H), 8.02 (d, $J = 5.1$ Hz, IH), 7.65-7.60 (m, 3H), 8.38 (s, IH), 9.35 (s, IH)

MS (ES+): $m/z$ 395 (M+H)$^+$

EXAMPLE 13 Preparation of 2-Chloro-4-(5-chloro-thiophen-2-yl)-5-methyl-pyrimidine (6)

$^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 1.65-1.72 (m, 4H), 2.10 (s, 3H), 2.18 (s, 3H), 2.50-2.58 (m, 4H), 2.78 (t, $J = 5.8$ Hz, 2H), 4.01 (t, $J = 6.0$ Hz, 2H), 6.85 (d, $J = 9.1$ Hz, 2H), 8.02 (d, $J = 5.1$ Hz, IH), 7.65-7.60 (m, 3H), 8.38 (s, IH), 9.35 (s, IH)

MS (ES+): $m/z$ 395 (M+H)$^+$
To a round bottomed flask was charged with 2,4-dichloro-5-methyl-pyrimidine (0.30 g, 1.84 mmol), S-chlorothiophene-boronic acid (0.40 g, 2.5 mmol) and Pd(PPh\(_3\))\(_4\) (0.15 g, 0.13 mmol). DMF (10 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 2.5 mL, 5.0 mmol). The reaction mixture was heated at 100 °C for 2 h. After cooling to room temperature, the mixture was filtered and the filtered solid washed with EtOAc. The filtrate was concentrated and the residue purified by column chromatography on silica gel (hexanes to 20% EtOAc/hexanes) to afford the title compound as a yellow solid (0.16 g, 36%).

**1H NMR** (500 MHz, DMSO\(_d_6\)): \(\delta\) 2.49 (s, 3H), 7.32 (d, \(J = 4.3\) Hz, 1H), 7.75 (d, \(J = 4.2\) Hz, 1H), 8.66 (s, 1H); **MS (ES+):** \(m/z\) 245 (M+H)+

**EXAMPLE 14: Preparation of [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine**

A suspension of 6 (50 mg, 0.20 mmol), 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (50 mg, 0.24 mmol), Pd\(_2\)(dba)\(_3\) (10 mg, 0.011 mmol), Xantphos (13 mg, 0.022 mmol) and cesium carbonate (0.15 g, 0.46 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 150 °C for 15 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO\(_3\) solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na\(_2\)SO\(_4\) and filtered. The filtrate was concentrated to afford the title compound as a brown solid (20 mg, 24%).

**1H NMR** (500 MHz, DMSO-d\(_6\)): \(\delta\) 1.65-1.75 (m, 4H), 2.37 (s, 3H), 2.50-2.60 (m, 4H), 2.78-2.83 (m, 2H), 4.05 (t, \(J = 5.9\) Hz, 2H), 6.91 (d, \(J = 9.0\) Hz, 2H), 7.26 (d, \(J = 4.3\) Hz, 1H),
EXAMPLE 15: Preparation of \{4-[5-(3-Isopropyl-phenyl)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl )-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{structure15.png}
\end{center}}
\]

[0156] EXAMPLE 16 Preparation of 5-(2-Chloro-5-methyl-pyrimidin-4-yl)-thiophene-2-carboxylic acid (7)
[0159] To a microwave reaction tube was charged with 2,4-dichloro-5-methyl-pyrimidine (0.50 g, 3.1 mmol), 5-(dihydroxyboryl)-2-thiophene carboxylic acid (0.65 g, 3.8 mmol) and Pd(PPh₃)₄ (0.20 g, 0.17 mmol). DMF (6 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 3.0 mL, 6.0 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 130 °C for 15 min. After cooling to room temperature, the mixture was poured into water (30 mL) and the pH adjusted to about 4. The mixture was extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue triturated in EtOAc. After filtration, the title compound was obtained as a pale yellow solid (0.25 g, 32%).

MS (ES+): m/z 255 (M+H)+

[0160] EXAMPLE 17 Preparation of 5-{5-Methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)phenylamino]-pyrimidin-4-yl}-thiophene-2-carboxylic acid

[0161] A suspension of 7 (0.10 g, 0.39 mmol), 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.10 g, 0.49 mmol), Pd₂(dba)₃ (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.26 g, 0.80 mmol) in dioxane (4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with a mixture of DCM/MeOH (5/1). The filtrate was concentrated and the residue purified by HPLC. The fractions were combined to afford the title compound as an orange solid (TFA salt; 70 mg, 33%). ¹H NMR
(500 MHz, DMSOd$_6$): $\delta$ 1.85-1.93 (m, 2H), 2.00-2.10 (m, 2H), 2.42 (s, 3H), 3.08-3.18 (m, 2H), 3.55-3.65 (m, 4H), 4.28 (t, $J = 5.0$ Hz, 2H), 7.00 (d, $J = 9.1$ Hz, 2H), 7.73 (d, $J = 9.1$ Hz, 2H), 7.77 (d, $J = 4.2$ Hz, 1H), 7.80 (d, $J = 4.2$ Hz, 1H), 8.43 (s, 1H), 9.50 (s, 1H), 9.70 (br s, 1H); MS (ES+): $m/z$ 425 (M+H)$^+$

**EXAMPLE 18** Preparation of [5-(2-Chloro-5-methyl-pyrimidin-4-yl)-thiophen-2-yl]-methanol (8)

![Chemical Structure](image)

[0162] To a microwave reaction tube was charged with 2,4-dichloro-5-methyl-pyrimidine (0.50 g, 3.1 mmol), 5-hydroxymethylthiophene-2-boronic acid (0.60 g, 3.8 mmol) and Pd(PPh$_3$)$_4$ (0.20 g, 0.17 mmol). DMF (6 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 3.0 mL, 6.0 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 140 °C for 15 min. After cooling to room temperature, the mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by column chromatography on silica gel (hexanes to 70% EtOAc/hexanes) to afford the title compound as an off white solid (0.16 g, 22%). MS (ES+): $m/z$ 241 (M+H)$^+$

**EXAMPLE 19** Preparation of (5-{5-Methyl-2-[4-(2-pyrrolidin-1-yl-methoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol

![Chemical Structure](image)
A suspension of 8 (0.10 g, 0.41 mmol), 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.10 g, 0.49 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (20 mg, 0.022 mmol), Xantphos (25 mg, 0.043 mmol) and cesium carbonate (0.26 g, 0.80 mmol) in dioxane (3 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO<sub>3</sub> solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a yellow solid (8 mg, 5%).<sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ 1.67-1.72 (m, 4H), 2.38 (s, 3H), 2.48-2.55 (m, 4H), 2.78-2.83 (m, 2H), 4.04 (t, J = 5.9 Hz, 2H), 4.69 (d, J = 5.8 Hz, 2H), 5.60 (t, J = 5.8 Hz, 1H), 6.88 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 3.9 Hz, 1H), 7.61 (d, J = 3.8 Hz, 1H), 7.69 (d, J = 9.1 Hz, 2H), 8.31 (s, 1H), 9.27 (s, 1H); MS (ES+): m/z 411 (M+H)<sup>+</sup>

**EXAMPLE 20** Preparation of N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-benzenesulfonamide

To a microwave reaction tube was charged with [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine (60 mg, 0.15 mmol), /N-methyl-3-boronobenzenesulfonamide (40 mg, 0.19 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (20 mg, 0.017 mmol). DMF (3 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.3 mL, 0.6 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The
fractions were combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a yellow solid (30 mg, 38%).

**1H NMR (500 MHz, DMSO-d₆):** δ 1.68-1.73 (m, 4H), 2.44 (s, 3H), 2.47 (d, J = 4.7 Hz, 3H), 2.50-2.60 (m, 4H), 2.78-2.85 (m, 2H), 4.05 (t, J = 5.9 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 7.59 (q, J = 4.8 Hz, IH), 7.68-7.78 (m, 5H), 7.81 (d, J = 4.2 Hz, IH), 8.05-8.09 (m, 2H), 8.37 (s, IH), 9.36 (s, IH); MS (ES+): m/z 550 (M+H)⁺

[0169] EXAMPLE 21 Preparation of N-tert-Butyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-benzenesulfonamide

[0169] To a microwave reaction tube was charged with [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine (60 mg, 0.15 mmol), N-tert-butyl-3-boronobenzenesulfonamide (45 mg, 0.18 mmol) and Pd(PPh₃)₄ (20 mg, 0.017 mmol). DMF (3 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.3 mL, 0.6 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a yellow solid (30
mg, 35%). \(^1\)H NMR (500 MHz, DMSO-d\(_6\)): \(\delta\) 1.14 (s, 9H), 1.65-1.72 (m, 4H), 2.44 (s, 3H), 2.50-2.60 (m, 4H), 2.78-2.88 (m, 2H), 4.05 (t, \(J = 5.8\) Hz, 2H), 6.92 (d, \(J = 9.0\) Hz, 2H), 7.60-7.75 (m, 5H), 7.80-7.83 (m, 2H), 8.02 (d, \(J = 8.0\) Hz, IH), 8.17 (t, \(J = U\) Hz, IH), 8.38 (s, IH), 9.37 (s, IH); MS (ES\(^+\)): \(m/z\) 592 (M+H)

[0170] EXAMPLE 22 Preparation of (5-Methyl-4-[5-[4-(2-pyrrolidin-1-yl-ethoxy)phenylamino]-thiophen-2-yl]-pyrimidin-2-yl)-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{S} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N}
\end{align*}
\]

[0171] A suspension of 6 (0.75 g, 3.1 mmol), 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.80 g, 3.9 mmol), \(\text{Pd}_2(\text{dba})_3\) (0.17 g, 0.19 mmol), Xantphos (0.22 g, 0.38 mmol) and cesium carbonate (2.0 g, 6.1 mmol) in dioxane (25 mL) was heated at reflux under argon atmosphere for 4 h. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by column chromatography on silica gel (DCM to 30% MeOH/DCM). The impure product was further purified by HPLC and the corrected fractions combined and poured into saturated NaHCO\(_3\) solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na\(_2\)SO\(_4\) and filtered. The filtrate was concentrated to afford the title compound as a greenish-yellow solid (14 mg, 1%).

[0172] \(^1\)H NMR (500 MHz, DMSO-d\(_6\)): \(\delta\) 1.60-1.72 (m, 8H), 2.32 (s, 3H), 2.48-2.58 (m, 8H), 2.80 (t, \(J = 5.8\) Hz, 4H), 4.02-4.06 (m, 4H), 6.44 (d, \(J = 4.1\) Hz, IH), 6.85 (d, \(J = 9.0\) Hz, 2H), 6.94 (d, \(J = 8.9\) Hz, 2H), 7.19 (d, \(J = 8.9\) Hz, 2H), 7.48 (d, \(J = 4.2\) Hz, IH), 7.68 (d, \(J = 9.0\) Hz, 2H), 8.13 (s, IH), 9.09 (s, IH), 9.28 (s, IH); MS (ES\(^+\)): \(m/z\) 585 (M+H)

EXAMPLE 23: Preparation of 5-(2-Chloro-5-methyl-pyrimidin-4-yl)-thiophene-2-carbonitrile (9)

To a microwave reaction tube was charged with 2,4-dichloro-5-methyl-pyrimidine (0.50 g, 3.1 mmol), 5-cyanothiophene-2-boronic acid (0.52 g, 3.4 mmol) and Pd(PPh$_3$)$_4$ (0.20 g, 0.17 mmol). DMF (6 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 2.0 mL, 4.0 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 120 °C for 20 min. After cooling to room temperature, the mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by column chromatography on silica gel (hexanes to 30% EtOAc/hexanes) to afford the title compound as an off white solid (70 mg, 10%). MS (ES+): m/z 236 (M+H)$^+$

EXAMPLE 24 Preparation of 5-{5-Methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl }-thiophene-2-carbonitrile

A suspension of 9 (70 mg, 0.30 mmol), 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (70 mg, 0.34 mmol), Pd$_2$(dba)$_3$ (15 mg, 0.016 mmol), Xantphos (20 mg, 0.035 mmol) and cesium carbonate (0.20 g, 0.61 mmol) in dioxane (6 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into
saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as an orange solid (20 mg, 17%). ¹H NMR (500 MHz, DMSO-d₆): δ 1.67-1.72 (m, 4H), 2.42 (s, 3H), 2.50-2.60 (m, 4H), 2.78-2.85 (m, 2H), 4.05 (t, J = 5.9 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 4.3 Hz, IH), 8.06 (d, J = 4.3 Hz, IH), 8.46 (s, IH), 9.49 (s, IH)

MS (ES+): m/z 406 (M+H)+

[0177] EXAMPLE 25: Preparation of {4-[5-(3,5-Dimethyl-isoxazol-4-yl)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl} {-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]} -amine

[0178] To a microwave reaction tube was charged with [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine (70 mg, 0.17 mmol), 3,5-dimethylisoxazole-4-boronic acid (30 mg, 0.21 mmol) and Pd(PPh₃)₄ (20 mg, 0.017 mmol). DMF (4 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.3 mL, 0.6 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a yellow solid (5 mg, 6%). ¹H NMR (500 MHz, DMSO-d₆): δ 1.67-1.72 (m, 4H), 2.40 (s, 3H), 2.42 (s, 3H),
2.50-2.60 (m, 4H), 2.60 (s, 3H), 2.78-2.88 (m, 2H), 4.04 (t, J = 5.8 Hz, 2H), 6.90 (d, J = 9.1 Hz, 2H), 7.35 (d, J = 4.0 Hz, IH), 7.60 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 4.0 Hz, IH), 8.36 (s, IH), 9.35 (s, IH) MS (ES+): m/z 476 (M+H)^+

[0179] EXAMPLE 26 Preparation of {5-Methyl-4-[5-(3-morpholin-4-yl-phenyl)-thiophen-2-yl]-pyrimidin-2-yl}-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine

![Chemical Structure](image)

[0180] To a microwave reaction tube was charged with [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine (55 mg, 0.13 mmol), 3-(morpholino)phenylboronic acid pinacol ester (45 mg, 0.16 mmol) and Pd(PPh₃)₄ (15 mg, 0.013 mmol). DMF (3 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.2 mL, 0.4 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a yellow solid (8 mg, 11%). ^1H NMR (500 MHz, DMSO-d₆): δ 1.65-1.70 (m, 4H), 2.42 (s, 3H), 2.46-2.56 (m, 4H), 2.79 (t, J = 5.7 Hz, 2H), 3.20 (t, J = 4.8 Hz, 4H), 3.78 (t, J = 4.8 Hz, 4H), 4.04 (t, J = 5.9 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 6.98 (dd, J = 8.3, 2.3 Hz, IH), 7.20 (d, J = 7.6 Hz, IH), 7.26 (s, IH), 7.33 (t, J = 8.0 Hz, IH), 7.63 (d, J = 4.0 Hz, IH), 7.71 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 4.0 Hz, IH), 8.34 (s, IH), 9.31 (s, IH) MS (ES+): m/z 542 (M+H)^+
EXAMPLE 27 Preparation of [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-
(4-morpholin-4-yl-phenyl)-amine

A suspension of 6 (0.10 g, 0.41 mmol), 4-morpholin-4-yl-phenylamine (80 mg, 0.45 mmol) and concentrated HCl (12 M; 0.1 mL, 1.2 mmol) in isopropanol (4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 170 °C for 30 min. After cooling to room temperature, the resulting mixture was poured into DCM (30 mL) and the organic layer washed with saturated NaHCO₃. The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue purified by column chromatography on silica gel (DCM to 5% MeOH/DCM) to afford the title compound as a yellow solid (75 mg, 48%).

¹H NMR (500 MHz, DMSO-d₆): δ 2.37 (s, 3H), 3.05 (t, J = 4.8 Hz, 4H), 3.74 (t, J = 4.7 Hz, 4H), 6.92 (d, J = 9.1 Hz, 2H), 7.26 (d, J = 4.0 Hz, IH), 7.50-7.60 (m, 3H), 8.34 (s, IH), 9.30 (s, IH)

MS (ES+): m/z 387 (M+H)⁺

EXAMPLE 28 Preparation of [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-(4-
imidazol-1-yl-phenyl)-amine

A suspension of 6 (0.20 g, 0.82 mmol), 4-imidazol-1-yl-phenylamine (0.15 g, 0.94 mmol), Pd₂dba₃ (40 mg, 0.044 mmol), Xantphos (50 mg, 0.086 mmol) and cesium carbonate (0.50 g, 1.53 mmol) in dioxane (6 mL) was sealed in a microwave reaction tube and irradiated...
with microwave at 160 °C for 20 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by column chromatography on silica gel (DCM to 25% MeOH/DCM) to afford the title compound as a creamy solid (0.15 g, 50%). 1H NMR (500 MHz, DMSO-d$_6$): δ 2.41 (s, 3H), 7.09 (s, 1H), 7.29 (d, J = 4.2 Hz, 1H), 7.61 (d, J = 8.9 Hz, 2H), 7.65 (d, J = 4.2 Hz, 1H), 7.71 (s, 1H), 7.90 (d, J = 8.9 Hz, 2H), 8.21 (s, 1H), 8.44 (s, 1H), 9.76 (s, 1H)

MS (ES+): m/z 368 (M+H)$^+$

[0185] EXAMPLE 29 Preparation of [4-[5-(3-Isopropyl-phenyl)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl]-(4-morpholin-4-yl-phenyl)-amine

To a microwave reaction tube was charged with [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-(4-morpholin-4-yl-phenyl)-amine (60 mg, 0.16 mmol), 3-isopropylphenyl boronic acid (35 mg, 0.21 mmol) and Pd(PPh$_3$)$_4$ (15 mg, 0.013 mmol). DMF (3 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.3 mL, 0.6 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 15 min. After cooling to room temperature, the mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO$_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na$_2$SO$_4$ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a yellow solid (20 mg, 27%). 1H NMR (500 MHz, DMSO-d$_6$): δ 1.27 (d, J = 6.9 Hz, 6H), 2.42 (s, 3H), 2.94-3.02 (m, 1H), 3.04 (t, J = 4.8 Hz, 4H), 3.74 (t, J = 4.7 Hz, 4H), 6.93 (d, / = 9.1 Hz, 2H), 7.27 (d, J = 1.9 Hz, IH), 7.40 (t, J =
7.7 Hz, IH), 7.58 (dd, J = 7.9, 0.9 Hz, IH), 7.61 (s, IH), 7.63 (d, J = 4.0 Hz, IH), 7.69 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 4.0 Hz, IH), 8.33 (s, IH), 9.26 (s, IH) MS (ES+): m/z 471 (M+H)+

[0187] EXAMPLE 30 Preparation of (4-Imidazol-l-yl-phenyl)-{4-[5-(3-isopropyl-phenyl)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl} -amine

To a microwave reaction tube was charged with [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-(4-imidazol-l-yl-phenyl)-amine (0.15 g, 0.41 mmol), 3-isopropylphenyl boronic acid (90 mg, 0.55 mmol) and Pd(PPh₃)₄ (50 mg, 0.043 mmol). DMF (3 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.5 mL, 1.0 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 25 min. After cooling to room temperature, the mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue further purified by column chromatography on silica gel (DCM to 20% MeOH/DCM) to afford the title compound as a yellow solid (5 mg, 3%). ¹H NMR (500 MHz, DMSO-d₆): δ 1.27 (d, J = 6.9 Hz, 6H), 2.46 (s, 3H), 2.94-3.02 (m, IH), 7.09 (s, IH), 7.28 (d, J = 1.1 Hz, IH), 7.41 (t, J = 1.1 Hz, IH), 7.59 (d, J = 8.9 Hz, 2H), 7.64 (s, IH), 7.66 (d, J = 10 Hz, IH), 7.68 (s, IH), 7.80 (d, J = 4.2 Hz, IH), 7.98 (d, J = 8.9 Hz, 2H), 8.17 (s, IH), 8.43 (s, IH), 9.72 (s, IH) MS (ES+): m/z 452 (M+H)+

[0188] To a microwave reaction tube was charged with [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-(4-imidazol-l-yl-phenyl)-amine (0.15 g, 0.41 mmol), 3-isopropylphenyl boronic acid (90 mg, 0.55 mmol) and Pd(PPh₃)₄ (50 mg, 0.043 mmol). DMF (3 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.5 mL, 1.0 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 25 min. After cooling to room temperature, the mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by column chromatography on silica gel (DCM to 20% MeOH/DCM) to afford the title compound as a yellow solid (5 mg, 3%). ¹H NMR (500 MHz, DMSO-d₆): δ 1.27 (d, J = 6.9 Hz, 6H), 2.46 (s, 3H), 2.94-3.02 (m, IH), 7.09 (s, IH), 7.28 (d, J = 1.1 Hz, IH), 7.41 (t, J = 1.1 Hz, IH), 7.59 (d, J = 8.9 Hz, 2H), 7.64 (s, IH), 7.66 (d, J = 10 Hz, IH), 7.68 (s, IH), 7.80 (d, J = 4.2 Hz, IH), 7.98 (d, J = 8.9 Hz, 2H), 8.17 (s, IH), 8.43 (s, IH), 9.72 (s, IH) MS (ES+): m/z 452 (M+H)+

[0189] EXAMPLE 31 Preparation of (5-Methyl-4-[5-[3-(morpholine-4-sulfonyl)-phenyl]-thiophen-2-yl]-pyrimidin-2-yl)-[4-(2-pyrrolidin-l-yl-ethoxy)-phenyl] -amine
To a microwave reaction tube was charged with [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine (50 mg, 0.12 mmol), 3-/V-morpholinylsulfonylphenyl boronic acid (45 mg, 0.17 mmol) and Pd(PPh₃)₄ (15 mg, 0.013 mmol). DMF (3 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.3 mL, 0.6 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 25 min. After cooling to room temperature, the mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a yellow solid (10 mg, 14%). ¹H NMR (500 MHz, DMSO-d₆): δ 1.63-1.73 (m, 4H), 2.44 (s, 3H), 2.50-2.62 (m, 4H), 2.78-2.88 (m, 2H), 2.95 (t, J = 4.6 Hz, 4H), 3.66 (t, J = 4.6 Hz, 4H), 4.05 (t, J = 5.9 Hz, 2H), 6.91 (d, J = 9.1 Hz, 2H), 7.71 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, IH), 7.78 (d, J = 7.7 Hz, IH), 7.80 (d, J = 4.0 Hz, IH), 7.82 (d, J = 4.1 Hz, IH), 7.99 (d, J = 1.6 Hz, IH), 8.38 (s, IH), 9.37 (s, IH); MS (ES+): m/z 606 (M+H)⁺
A suspension of [(4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl)-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine (55 mg, 0.13 mmol), aniline (0.02 mL, 0.22 mmol), Pd$_2$(dba)$_3$ (10 mg, 0.011 mmol), Xantphos (15 mg, 0.026 mmol) and cesium carbonate (0.10 g, 0.31 mmol) in dioxane (4 mL) was sealed in a microwave reaction tube and irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO$_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na$_2$SO$_4$ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a yellow solid (10 mg, 16%).

$^1$H NMR (500 MHz, DMSO-d$_6$): δ 1.65-1.73 (m, 4H), 2.34 (s, 3H), 2.50-2.60 (m, 4H), 2.78-2.85 (m, 2H), 4.04 (t, J = 5.9 Hz, 2H), 6.60 (d, J = 4.2 Hz, IH), 6.86 (d, J = 9.0 Hz, 2H), 7.92 (t, J = 7.3 Hz, IH), 7.24 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.52 (d, J = 4.3 Hz, IH), 7.69 (d, J = 9.0 Hz, 2H), 8.17 (s, IH), 9.13 (s, IH), 9.45 (s, IH)

MS (ES+): m/z ML (M+H)$^+$

**EXAMPLE 33** Preparation of 4-(5-Bromo-thiophen-2-yl)-2-chloro-5-methyl-pyrimidine (10)

![Chemical Structure](image)

To a round bottomed flask was charged with 2,4-dichloro-5-methyl-pyrimidine (2.0 g, 12.3 mmol), 5-bromothiophene-2-boronic acid (2.6 g, 12.6 mmol) and Pd(PPh$_3$)$_4$ (1.0 g, 0.87 mmol). DMF (15 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 7.0 mL, 14 mmol). The reaction mixture was heated at 110 °C for 4 h. After cooling to room temperature, the mixture was filtered and the filtered solid washed with EtOAc. The
filtrate was washed with water (2 x 40 mL) and brine. The organic layer was separated, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue purified by column chromatography on silica gel (hexanes to 20% EtOAc/hexanes) to afford the title compound as a light brown solid (0.20 g, 6%).

**EXAMPLE 34** [4-(5-Bromo-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine (11)

![Chemical Structure](image)

**MS (ES+): m/z 289, 291 (M+H)^+**

**EXAMPLE 35** Preparation of {5-Methyl-4-[5-(3-piperazin-1-yl-phenyl)-thiophen-2-yl]-pyrimidin-2-yl}-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine

A suspension of 10 (0.20 g, 0.69 mmol), 4-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (0.20 g, 0.97 mmol) and concentrated HCl (12 M; 0.2 mL, 2.4 mmol) in isopropanol (6 mL) was sealed in a microwave reaction tube and irradiated with microwave at 170 °C for 45 min. After cooling to room temperature, the resulting mixture was concentrated. The residue was taken up in EtOAc and the organic layer washed with saturated NaHCO₃. The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue purified by column chromatography on silica gel (DCM to 20% MeOH/DCM) to afford the title compound (0.23 g, 72%).

**MS (ES+): m/z 459, 461 (M+H)^+**
To a microwave reaction tube was charged with 11 (70 mg, 0.15 mmol), 4-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester (70 mg, 0.18 mmol) and Pd(PPh₃)₄ (20 mg, 0.017 mmol). DMF (3 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.3 mL, 0.6 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue suspended in a mixture of DCM/TFA (5/3, 8 mL). The mixture was stirred at 60 °C for 1 h and then concentrated. The crude product was purified by HPLC, the corrected fractions combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a yellow solid (25 mg, 30% in 2 steps). ¹H NMR (500 MHz, DMSO-d₆): δ 1.60-1.70 (m, 4H), 2.42 (s, 3H), 2.48-2.55 (m, 4H), 2.78 (t, J = 5.9 Hz, 2H), 2.90 (t, J = 5.0 Hz, 4H), 3.16 (t, J = 5.0 Hz, 4H), 4.03 (t, J = 6.0 Hz, 2H), 6.90 (d, J = 9.1 Hz, 2H), 6.96 (dd, J = 8.3, 2.1 Hz, IH), 7.17 (d, J = 8.0 Hz, IH), 7.24 (s, IH), 7.30 (t, J = 8.0 Hz, IH), 7.62 (d, J = 4.0 Hz, IH), 7.71 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 4.0 Hz, IH), 8.34 (s, IH), 9.31 (s, IH)MS (ES+): m/z 541 (M+H)+

EXAMPLE 36 Preparation of [4-(5-Isoxazol-4-yl-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine
[0200] To a microwave reaction tube was charged with 11 (70 mg, 0.15 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isoxazole (40 mg, 0.21 mmol) and Pd(PPh₃)₄ (15 mg, 0.013 mmol). DMF (3 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.3 mL, 0.6 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a brown solid (10 mg, 15%). ¹H NMR (500 MHz, DMSO-d₆): δ 1.75-1.85 (m, 4H), 2.33 (s, 3H), 2.42 (s, 3H), 2.80-3.00 (m, 4H), 3.10-3.20 (m, 2H), 4.10-4.20 (m, 2H), 6.65 (d, J = 4.1 Hz, IH), 6.90 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 4.2 Hz, IH), 7.77 (d, J = 9.0 Hz, 2H), 8.10 (s, IH), 8.71 (s, IH), 9.07 (s, IH) MS (ES+): m/z 448 (M+H)⁺

[0201] EXAMPLE 37 Preparation of \{4-[5-(1-Isobutyl-1H-pyrazol-4-yl)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl \}-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine
To a microwave reaction tube was charged with 11 (50 mg, 0.11 mmol), 1-isobutyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (40 mg, 0.16 mmol) and Pd(PPh₃)₄ (20 mg, 0.017 mmol). DMF (3 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.3 mL, 0.6 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a brown solid (25 mg, 46%).

[0203] ¹H NMR (500 MHz, DMSO-d₆): δ 0.87 (d, J = 6.8 Hz, 6H), 1.65-1.72 (m, 4H), 2.10-2.20 (m, IH), 2.40 (s, 3H), 2.50-2.60 (m, 4H), 2.80 (t, J = 5.6 Hz, 2H), 3.96 (d, J = 7.3 Hz, 2H), 4.05 (t, J = 5.9 Hz, 2H), 6.93 (d, J = 9.1 Hz, 2H), 7.31 (d, J = 3.9 Hz, IH), 7.68 (d, J = 4.0 Hz, IH), 7.71 (d, J = 9.0 Hz, 2H), 7.87 (s, IH), 8.20 (s, IH), 8.30 (s, IH), 9.28 (s, IH)

MS (ES+): m/z 503 (M+H)⁺

[0204] EXAMPLE 38 Preparation of {4-[5-(2,4-Dimethyl-thiazol-5-yl)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl }-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine

[0205] To a microwave reaction tube was charged with [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine (70 mg, 0.17 mmol), 2,4-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiazole (60 mg, 0.25 mmol) and
Pd(PPh₃)₄ (20 mg, 0.017 mmol). DMF (4 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 0.3 mL, 0.6 mmol). The reaction tube was sealed and the suspension irradiated with microwave at 160 °C for 20 min. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a yellow solid (28 mg, 34%).

[0206] ¹H NMR (500 MHz, DMSO-d₆): δ 1.65-1.72 (m, 4H), 2.41 (s, 3H), 2.50-2.60 (m, 4H), 2.55 (s, 3H), 2.64 (s, 3H), 2.78-2.83 (m, 2H), 4.04 (t, J = 5.9 Hz, 2H), 6.89 (d, J = 9.1 Hz, 2H), 7.30 (d, J = 4.0 Hz, IH), 7.69 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 4.0 Hz, IH), 8.35 (s, IH), 9.34 (s, IH)

[0207] MS (ES+): m/z 492 (M+H)+

[0208] EXAMPLE 39 Preparation of {4-[5-(3-fer?-Butyl-phenylamino)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl}-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine

[0209] A suspension of [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine (0.10 g, 0.24 mmol), 3-te/t-butyl-phenylamine (50 mg, 0.31 mmol), Pd₂(dba)₃ (15 mg, 0.016 mmol), Xantphos (20 mg, 0.035 mmol) and cesium carbonate (0.16 g, 0.49 mmol) in dioxane (6 mL) was heated at 140 °C under argon atmosphere for 2 h. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by
HPLC. The fractions were combined and poured into saturated NaHCO$_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na$_2$SO$_4$ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a light brown solid (25 mg, 20%).

[0210] $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 1.29 (s, 9H), 1.65-1.72 (m, 4H), 2.34 (s, 3H), 2.48-2.58 (m, 4H), 2.78-2.83 (m, 2H), 4.02 (t, $J =$ 6.0 Hz, 2H), 6.58 (d, $J =$ 4.2 Hz, IH), 6.85 (d, $J =$ 9.1 Hz, 2H), 6.97 (d, $J =$ 7.9 Hz, IH), 7.08 (dd, $J =$ 7.7, 2.3 Hz, IH), 7.23 (t, $J =$ 2.0 Hz, IH), 7.26 (t, $J =$ 7.9 Hz, IH), 7.52 (d, $J =$ 4.3 Hz, IH), 7.68 (d, $J =$ 9.1 Hz, 2H), 8.17 (s, IH), 9.13 (s, IH), 9.47 (s, IH)

[0211] MS (ES+): $m/z$ 528 (M+H)$^+$

[0212] EXAMPLE 40 Preparation of N-te/t-Butyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-l-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-ylamino)-benzenesulfonamide

[0213] A suspension of [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-l-yl-ethoxy)-phenyl] -amine (0.10 g, 0.24 mmol), 3-amino-/V-te/t-butyl-benzenesulfonamide (75 mg, 0.33 mmol), Pd$_2$(dba)$_3$ (15 mg, 0.016 mmol), Xanthphos (20 mg, 0.035 mmol) and cesium carbonate (0.16 g, 0.49 mmol) in dioxane (6 mL) was heated at 150 °C under argon atmosphere for 2 h. After cooling to room temperature, the resulting mixture was filtered and the filtered solid washed with DCM. The filtrate was concentrated and the residue purified by HPLC. The fractions were combined and poured into saturated NaHCO$_3$ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and
the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue re-dissolved in minimum amount of EtOAc and hexanes added until solid precipitated. After filtration, the title compound was obtained as a brown solid (20 mg, 14%).

[0214] ¹H NMR (500 MHz, DMSO-d₆): δ 1.11 (s, 9H), 1.65-1.72 (m, 4H), 2.37 (s, 3H), 2.48-2.58 (m, 2H), 2.78-2.83 (m, 2H), 4.03 (t, J = 5.9 Hz, 2H), 6.71 (d, J = 4.2 Hz, IH), 6.88 (d, J = 9.1 Hz, 2H), 7.33 (d, J = 7.1 Hz, IH), 7.35 (dd, J = 7.7, 2.5 Hz, IH), 7.48 (t, J = 7.9 Hz, IH), 7.55 (s, IH), 7.57 (d, J = 4.3 Hz, IH), 7.65 (t, J = 2.0 Hz, IH), 7.68 (d, J = 9.0 Hz, 2H), 8.22 (s, IH), 9.17 (s, IH), 9.68 (s, IH)

[0215] MS (ES+): m/z 607 (M+H)⁺

[0216] EXAMPLE 41 Preparation of 4-(Benzo[b]thiophen-2-yl)-2-chloro-5-methylpyrimidine (12)

[0217] To a solution of 2,4-dichloro-5-methylpyrimidine (386 mg, 2.3 mmol) in dimethoxyethane (DME, 10 mL) was added a solution of benzo[b]thiophen-2-yl-2-boronic acid (463 mg, 2.6 mmol) in EtOH (5 mL), 2.0 M Na₂CO₃ (4 mL), and tetrakis(triphenylphosphine)palladium (0) (Pd(PPh₃)₄, 230 mg, 0.2 mmol). The reaction mixture was heated at 110 °C for 20 min under µ-wave. The hot solution was filtered and the solid washed with EtOAc. The filtrate was washed with brine (100 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). Combined organic layer was dried (Na₂SO₄). The solvent was removed in vacuo and the crude material (570 mg, 95%) used for next reaction without further purification.

[0218] EXAMPLE 42 Preparation of 4-(Benzo[f]thiophen-2-yl)-5-methyl-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine
To a solution of 12 (570 mg, 2.2 mmol) in 1,4-dioxane (100 mL) was added 4-(4-methylpiperazin-1-yl)benzenamine (418 mg, 2.2 mmol), Cs₂CO₃ (2.6 g, 8.0 mmol), Pd₂(dba)₃ (182 mg, 0.2 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xantphos, 347 mg, 0.6 mmol). The mixture was heated under reflux overnight under Ar. The solid was filtered off and the filtrate was washed with brine (1 x 100 mL). The organic solution was separated and dried (Na₂SO₄). The solvent was removed in vacuo. The crude product purified by using HPLC. The HPLC fractions containing product were combined and neutralized with saturated NaHCO₃ (50 mL). The free base was extracted with EtOAc (2 x 100 mL). The organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The residue was dissolved in MeOH (2 mL) and 4.0 M HCl solution (1.0 mL, 4.0 mmol) in dioxane was added. The solution was stirred for 5 min at room temperature and then the solvent was removed in vacuo. The residue was dissolved in MeOH (1 mL) and anhydrous Et₂O (20 mL) was added. The solid was collected by centrifuging. The title compound (227 mg, 23%) was afforded as a yellow solid.

[0219] ¹H NMR (500 MHz, DMSO-d₆): δ 2.52 (s, 3H), 2.81 (d, J = 4.0 Hz, 3H), 3.09-3.21 (m, 4H), 3.49 (d, J = 11.4 Hz, 2H), 3.74 (d, J = 12.5 Hz, 2H), 7.04 (d, J = 9.1 Hz, 2H), 7.42-7.49 (m, 2H), 7.75 (d, J = 9.1 Hz, 2H), 8.00 (dd, J = 7.0, 1.5 Hz, IH), 8.04 (d, J = 7.6 Hz, IH), 8.17 (s, IH), 8.43 (s, IH), 9.56 (s, IH), 11.04 (br s, IH)

[0220] MS (ES⁺): m/z 416 (M+H)+

[0222] EXAMPLE 43 Preparation of N-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenyl)-4-(benzo[b]thiophen-2-yl)-5-methylpyrimidin-2-amine
To a solution of 12 (261 mg, 1.0 mmol) in 1,4-dioxane (50 mL) was added 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (206 mg, 1.0 mmol), Cs₂CO₃ (1.3 g, 4.0 mmol), Pd₂(dba)₃ (92 mg, 0.1 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xantphos, 170 mg, 0.3 mmol). The mixture was heated under reflux overnight under Ar. The solid was filtered off and the filtrate was washed with brine (1 x 100 mL). The organic solution was separated and dried (Na₂SO₄). The solvent was removed in vacuo. The crude product was purified by using HPLC. The HPLC fractions containing product were combined and neutralized with saturated NaHCO₃ (50 mL). The free base was extracted with EtOAc (2 x 100 mL). The organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The residue was dissolved in MeOH (2 mL) and 4.0 M HCl solution (1.0 mL, 4.0 mmol) in dioxane was added. The solution was stirred for 5 min at room temperature and then the solvent removed in vacuo. The residue was dissolved in MeOH (1 mL) and anhydrous Et₂O (20 mL) was added. The solid was collected by centrifuging. The title compound (14 mg, 3%) was afforded as a yellow solid.

[0224] ¹H NMR (500 MHz, DMSO-d₆): δ 1.87-1.92 (m, 2H), 1.99-2.04 (m, 2H), 2.52 (s, 3H), 3.08-3.13 (m, 2H), 3.55-3.60 (m, 4H), 4.35 (t, J = 5.0 Hz, 2H), 7.02 (d, J = 9.1 Hz, 2H), 7.42-7.48 (m, 2H), 7.79 (d, J = 9.1 Hz, 2H), 8.00 (dd, J = 6.8, 1.5 Hz, IH), 8.04 (d, J = 7.6 Hz, IH), 8.16 (s, IH), 8.44 (s, IH), 9.56 (s, IH), 10.83 (br s, IH)

[0225] MS (ES+): m/z 431 (M+H)⁺

[0226] EXAMPLE 44 Preparation of 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(4-(piperidin-4-yl oxy)phenyl)pyrimidin-2-amine
[0227] To a solution of 12 (70 mg, 0.26 mmol) in 1,4-dioxane (30 mL) was added tert-butyl A-(4-aminophenoxy)piperidine-1-carboxylate (78 mg, 0.26 mmol), Cs₂CO₃ (326 mg, 1.0 mmol), Pd₂(dba)₃ (18 mg, 0.02 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene (Xantphos, 30 mg, 0.06 mmol). The mixture was heated under reflux overnight under Ar. The solid was filtered off and the filtrate washed with brine (1 x 30 mL). The organic solution was separated and dried (Na₂SO₄). The solvent was removed in vacuo. The residue was dissolved in CH₂Cl₂ (10 mL) and treated with trifluoroacetic acid (1 mL). The mixture was stirred for 2 h at room temperature. The 10% NaOH was added until basic. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The crude product was purified by using HPLC. The HPLC fractions containing product were combined and neutralized with saturated NaHCO₃ (20 mL). The free base was extracted with EtOAc (2 x 30 mL). The organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The residue was dissolved in MeOH (2 mL) and 4.0 M HCl solution (0.2 mL, 0.8 mmol) in dioxane was added. The solution was stirred for 5 min at room temperature and then the solvent removed in vacuo. The residue was dissolved in MeOH (1 mL) and anhydrous Et₂O (20 mL) was added. The solid was collected by centrifuging. The title compound (14 mg, 12%) was afforded as a yellow solid.

[0228] ³H NMR (500 MHz, DMSO-d₆): δ 1.81-1.87 (m, 2H), 1.90-2.21 (m, 2H), 2.52 (s, 3H), 3.07 (br s, 2H), 3.23 (br s, 2H), 4.57-4.59 (m, 1H), 7.00 (d, J = 9.0 Hz, 2H), 7.43-7.48 (m, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.99 (d, J = 6.8 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 8.15 (s, 1H), 8.43 (s, 1H), 8.84 (br s, 1H), 8.90 (br s, 1H), 9.49 (s, 1H)

[0229] MS (ES+): m/z All (M+H)⁺

[0230] EXAMPLE 45 Preparation of 4-(Benzo[b]thiophen-2-yl)-5-methyl- N-(3-(piperazin-1-yl)phenyl)pyrimidin-2-amine
To a solution of 12 (50 mg, 0.19 mmol) in 1,4-dioxane (30 mL) was added tert-butyl A-(3-aminophenyl)piperazine-1-carboxylate (53 mg, 0.19 mmol), Cs₂CO₃ (326 mg, 1.0 mmol), Pd₂(dba)₃ (18 mg, 0.02 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 30 mg, 0.06 mmol). The mixture was heated under reflux overnight under Ar. The solid was filtered off and the filtrate was washed with brine (1 x 30 mL). The organic solution was separated and dried (Na₂SO₄). The solvent was removed in vacuo. The residue was dissolved in CH₂Cl₂ (10 mL) and treated with trifluoroacetic acid (1 mL). The mixture was stirred for 2 h at room temperature. The 10% NaOH was added until basic. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The crude product was purified by using HPLC. The HPLC fractions containing product were combined and neutralized with saturated NaHCO₃ (20 mL). The free base was extracted with EtOAc (2 x 30 mL). The organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The residue was dissolved in MeOH (2 mL) and 4.0 M HCl solution (0.2 mL, 0.8 mmol) in dioxane was added. The solution was stirred for 5 min at room temperature and then the solvent was removed in vacuo. The residue was dissolved in MeOH (1 mL) and anhydrous Et₂O (20 mL) was added. The solid was collected by centrifuging. The title compound (12 mg, 14%) was afforded as a yellow solid.

[0232] ¹H NMR (500 MHz, DMSO-d₆): δ 2.54 (s, 3H), 3.27-3.30 (m, 4H), 3.44-3.46 (m, 4H), 6.64 (dd, J = 8.1, 1.9 Hz, IH), 7.21 (t, J = 8.1 Hz, IH), 7.29 (dd, J = 8.0, 1.2 Hz, IH), 7.43-7.48 (m, 2H), 7.72 (s, IH), 8.00 (dd, J = 6.7, 1.7 Hz, IH), 8.10 (d, J = 7.5 Hz, IH), 8.18 (s, IH), 8.48 (s, IH), 9.38 (br s, 2H), 9.62 (s, IH); MS (ES+): m/z 402 (M+H)⁺

[0233] EXAMPLE 46 Preparation of 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(4-(2-methyl-1 H-imidazol-1-yl)phenyl) pyrimidin-2-amine
To a solution of 12 (160 mg, 0.61 mmol) in 1,4-dioxane (30 mL) was added 4-(2-
methyl-l H-imidazol-l-yl)benzenamine (106 mg, 0.61 mmol), Cs$_2$CO$_3$ (782 mg, 2.4 mmol),
Pd$_2$(dba)$_3$ (50 mg, 0.06 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethyxanthene
(Xantphos, 100 mg, 0.18 mmol). The mixture was heated under reflux overnight under Ar.
The solid was filtered off and the filtrate washed with brine (1 x 30 mL). The organic solution
was separated and dried (Na$_2$SO$_4$). The solvent was removed in vacuo. The crude product
was purified by using HPLC. The HPLC fractions containing product were combined and
neutralized with saturated NaHCO$_3$ (20 mL). The free base was extracted with EtOAc (2 x 30
mL). The organic layers were combined and dried (Na$_2$SO$_4$). The solvent was removed in
vacuo. The residue was dissolved in MeOH (2 mL) and 4.0 M HCl solution (0.2 mL, 0.8
mmol) in dioxane was added. The solution was stirred for 5 min at room temperature and then
the solvent removed in vacuo. The residue was dissolved in MeOH (1 mL) and anhydrous
Et$_2$O (20 mL) was added. The solid was collected by centrifuging. The title compound (68
mg, 26%) was afforded as a yellow solid.

$^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 2.56 (s, 3H), 2.57 (s, 3H), 7.44-7.49 (m, 2H), 7.60
(d, $J = 8.9$ Hz, 2H), 7.77 (d, $J = 2.0$ Hz, IH), 7.87 (d, $J = 2.0$ Hz, IH), 8.01-8.03 (m, 2H), 8.11
(d, $J = 8.9$ Hz, 2H), 8.20 (s, IH), 8.54 (s, IH), 10.07 (s, IH), 15.02 (br s, IH); MS (ES+): $m/z$
398 (M+H)$^+$

EXAMPLE 47 Preparation of 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(6-(piperazin-1-
yl)pyridin-3-yl)pyrimidin-2-amine
To a solution of 12 (210 mg, 0.8 mmol) in 1,4-dioxane (50 mL) was added tert-butyl A-(5-aminopyridin-2-y)l)pipazaine-1-carboxylate (224 mg, 0.8 mmol), Cs₂CO₃ (1 g, 3.2 mmol), Pd₂(dba)₃ (74 mg, 0.08 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethoxanthene (Xantphos, 150 mg, 0.24 mmol). The mixture was heated under reflux overnight under Ar. The solid was filtered off and the filtrate washed with brine (1 x 30 mL). The organic solution was separated and dried (Na₂SO₄). The solvent was removed in vacuo. The solid was dissolved in CH₂Cl₂ (10 mL) and treated with trifluoroactic acid (1 mL). The mixture was stirred for 2 h at room temperature. The 10% NaOH was added until basic. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The crude product was purified by using HPLC. The HPLC fractions containing product were combined and neutralized with saturated NaHCO₃ (20 mL). The free base was extracted with EtOAc (2 x 30 mL). The organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The residue was dissolved in MeOH (2 mL) and 4.0 M HCl solution (0.4 mL, 1.6 mmol) in dioxane was added. The solution was stirred for 5 min at room temperature and then the solvent removed in vacuo. The residue was dissolved in MeOH (1 mL) and anhydrous Et₂O (20 mL) was added. The solid was collected by centrifuging. The title compound (62 mg, 18%) was afforded as a yellow solid.

[0238] ¹H NMR (500 MHz, DMSO-d₆): δ 2.54 (s, 3H), 3.26 (br s, 4H), 3.89 (br s, 4H), 7.35 (br s, IH), 7.43-7.49 (m, 2H), 8.01-8.03 (m, 2H), 8.19 (s, IH), 8.21 (d, J = 7.7 Hz, IH), 8.83 (br s, IH), 9.44 (br s, 2H), 9.84 (br s, IH); MS (ES+): m/z 403 (M+H)⁺

[0239] EXAMPLE 48: Preparation of 2-Chloro-5-methyl-4-(5-methyl-benzo[£]thiophen-2-y)l)pyrimidine (13)
[0240] To a solution of 2,4-dichloro-5-methylpyrimidine (163 mg, 1.0 mmol) in dimethoxyethane (DME, 20 mL) was added a solution of 5-methyl-benzo[b]thiophen-2-yl-2-boronic acid (211 mg, 1.1 mmol) in EtOH (10 mL), 1.0 M Na₂CO₃ (4 mL), and tetrakis(triphenylphosphine)palladium (0) (Pd(PPh₃)₄, 115 mg, 0.1 mmol). The reaction mixture was heated at 110 °C for 20 min under µ-wave. The hot solution was filtered and the solid washed with EtOAc. The filtrate was washed with brine (100 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). Combined organic layer was dried (Na₂SO₄). The solvent was removed in vacuo and the crude material purified by flash column (SiO₂/EtOAc:Hexanes = 1:1). The title compound (210 mg, 78%) was afforded as a white solid.

[0241] EXAMPLE 49 Preparation of 5-Methyl-4-(5-methylbenzo[b]thiophen-2-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine

[0242] To a solution of 13 (90 mg, 0.32 mmol) in 1,4-dioxane (20 mL) was added A-(A-methylpiperazin-1-yl)benzenamine (63 mg, 0.32 mmol), Cs₂CO₃ (391 mg, 1.2 mmol), Pd₂(dba)₃ (27 mg, 0.03 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 58 mg, 0.1 mmol). The mixture was heated under reflux overnight under Ar. The solid was filtered off and the filtrate washed with brine (1 x 50 mL). The organic solution was separated and dried (Na₂SO₄). The solvent was removed in vacuo. The crude product was
purified by using HPLC. The HPLC fractions containing product were combined and neutralized with saturated NaHCO₃ (20 mL). The free base was extracted with EtOAc (2 x 30 mL). The organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The residue was dissolved in MeOH (2 mL) and 4.0 M HCl solution (0.1 mL, 0.4 mmol) in dioxane was added. The solution was stirred for 5 min at room temperature and then the solvent removed in vacuo. The residue was dissolved in MeOH (1 mL) and anhydrous Et₂O (20 mL) was added. The solid was collected by centrifuging. The title compound (10 mg, 7%) was afforded as a yellow solid. ¹H NMR (500 MHz, DMSO-d₆): δ 2.44 (s, 3H), 2.52 (s, 3H), 2.81 (d, J = 4.0 Hz, 3H), 3.06-3.11 (m, 2H), 3.14-3.18 (m, 2H), 3.49 (d, J = 12.4 Hz, 2H), 3.74 (d, J = 12.9 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 8.2 Hz, IH), 7.75 (d, J = 9.0 Hz, 2H), 7.78 (s, IH), 7.91 (d, J = 8.2 Hz, IH), 8.07 (s, IH), 8.42 (s, IH), 9.53 (s, IH), 10.89 (br s, IH) MS (ES+): m/z 430 (M+H)+

[0243] EXAMPLE 50 Preparation of N-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenyl)-5-methyl-4-(5-methylbenzo[b]thiophen-2-yl)pyrimidin-2-amine

[0244] To a solution of 13 (110 mg, 0.4 mmol) in 1,4-dioxane (20 mL) was added 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (83 mg, 0.4 mmol), Cs₂CO₃ (500 mg, 1.6 mmol), Pd₂(dba)₃ (46 mg, 0.05 mmol), and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 90 mg, 0.15 mmol). The mixture was heated under reflux overnight under Ar. The solid was filtered off and the filtrate washed with brine (1 x 50 mL). The organic solution was separated and dried (Na₂SO₄). The solvent was removed in vacuo. The crude product was purified by using HPLC. The HPLC fractions containing product were combined and neutralized with saturated NaHCO₃ (20 mL). The free base was extracted with EtOAc (2 x 30 mL). The organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The residue was dissolved in MeOH (2 mL) and 4.0 M HCl solution (0.15 mL, 0.6 mmol) in dioxane was added. The solution was stirred for 5 min at room temperature and then
the solvent removed in vacuo. The residue was dissolved in MeOH (1 mL) and anhydrous Et$_2$O (20 mL) was added. The solid was collected by centrifuging. The title compound (20 mg, 10%) was afforded as a yellow solid. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 1.87-1.92 (m, 2H), 1.99-2.04 (m, 2H), 2.44 (s, 3H), 2.52 (s, 3H), 3.08-3.15 (m, 2H), 3.55-3.60 (m, 4H), 4.34 (t, $J$ = 5.0 Hz, 2H), 7.02 (d, $J$ = 9.0 Hz, 2H), 7.30 (dd, $J$ = 8.3, 1.3 Hz, 1H), 7.77 (d, $J$ = 9.0 Hz, 2H), 7.78 (s, 1H), 7.91 (d, $J$ = 8.2 Hz, 1H), 8.06 (s, 1H), 8.42 (s, 1H), 9.54 (s, 1H), 10.81 (br s, 1H) MS (ES+): $m/z$ 445 (M+H)$^+$

[0245] EXAMPLE 51 Preparation of 2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-ol (14)

[0246] A mixture of 5-methyl-2-(methylthio)pyrimidin-4-ol (10 g, 0.064 mol) and 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (21 g, 0.103 mol) in DMEU (150 mL) was heated to reflux (170°C) for 72 h. After cooled to room temperature, IN HCl (500 mL) and Et$_2$O (400 mL) were added and stirred for 10 min. The aqueous layer was washed with EtOAc (2 x 200 mL) and basified with K$_2$CO$_3$ to pH-10. The mixture was extracted with EtOAc (2 x 200 mL), concentrated in vacuo and purified by column chromatography (silica, elute; DCM:MeOH=20:1~ DCM:MeOH=10:1) to afford the compound (11 g, 60%) as a white solid.

[0247] EXAMPLE 52 Preparation of N-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenyl)-4-chloro-5-methylpyrimidin-2-amine (15)

[0248] To a stirred solution of 14 (18 g, 0.06 mol) in MeCN (1000 mL) was added drop wise HCl/dioxane (4 N, 40 mL). After stirred for 10 min, POCl$_3$ (150 mL) was added drop wise. The stirred mixture was heated to reflux (83°C) overnight. The mixture was cooled to room
temperature and the solvent removed in vacuo. The residue was added ice-water (300 mL) and basified with NaOH (4 N) to pH=11-12. The mixture was extracted with CHCl₃ (300 mL x 3), dried with Na₂SO₄ and concentrated in vacuo to give crude product, which was purified by column chromatography (silica, elute; DCM: MeOH=20:1~ DCM:MeOH=10:1) to afford the title compound (11 g, 50%) as a white solid.

[0249] EXAMPLE 53 Preparation of 2-(2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-yl)benzo[ b]thiophene-6-carbonitrile

![Chemical structure]

[0250] To a solution of 15 (167 mg, 0.5 mmol) in dimethoxyethane (DME, 10 mL) was added a solution of 6-cyanobenzo[ b]thiophen-2-yl-2-boronic acid (117 mg, 0.55 mmol) in EtOH (5 mL), 2.0 M Na₂CO₃ (1.0 mL), and tetrakis(triphenylphosphine)palladium (0) (Pd(PPh₃)₄, 58 mg, 0.05 mmol). The reaction mixture was heated at 110 °C for 20 min under μ-wave. The hot solution was filtered and the solid washed with EtOAc. The organic solution was separated and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organic layer was dried (Na₂SO₄). The solution was removed in vacuo. The crude product was purified by using HPLC. The HPLC fractions containing product were combined and neutralized with saturated NaHCO₃ (50 mL). The free base was extracted with EtOAc (2 x 100 mL). The organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The residue was dissolved in MeOH (2 mL) and 4.0 M HCl solution (0.3 mL, 1.2 mmol) in dioxane was added. The solution was stirred for 5 min at room temperature and then the solvent removed in vacuo. The residue was dissolved in MeOH (1 mL) and anhydrous Et₂O (20 mL) was added. The solid was collected by centrifuging. The title compound (42 mg, 17%) was afforded as a yellow solid. ¹H NMR (500 MHz, DMSO-d₆): δ 1.87-1.92 (m, 2H), 1.99-2.06 (m, 2H), 2.53 (s, 3H), 3.09-3.16 (m, 2H), 3.56-3.62 (m, 4H), 4.33 (t, J = 4.9 Hz, 2H), 7.01 (d, J = 9.2 Hz, 2H), 7.77 (d, J = 9.2 Hz, 2H), 7.81 (dd, J = 8.4, 1.5 Hz, IH), 8.17 (d, J = 8.4 Hz, IH),
EXAMPLE 54 Preparation of 2-(2-(4-(2-((Pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-yl)benzo[ b]thiophene-7-carbonitrile

[0251] To a solution of 15 (167 mg, 0.5 mmol) in dimethoxyethane (DME, 10 mL) was added a solution of 7-cyanobenzo[ b]thiophen-2-yl-2-boronic acid (117 mg, 0.55 mmol) in EtOH (5 mL), 2.0 M Na₂CO₃ (1.0 mL), and tetrakis(triphenylphosphine)palladium (0) (Pd(PPh₃)₄, 58 mg, 0.05 mmol). The reaction mixture was heated at 110 °C for 20 min under µ-wave. The hot solution was filtered and the solid washed with EtOAc. The organic solution was separated and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organic layer was dried (Na₂SO₄). The solvent was removed in vacuo. The crude product was purified by using HPLC. The HPLC fractions containing product were combined and neutralized with saturated NaHCO₃ (50 mL). The free base was extracted with EtOAc (2 x 100 mL). The organic layers were combined and dried (Na₂SO₄). The solvent was removed in vacuo. The residue was dissolved in MeOH (2 mL) and 4.0 M HCl solution (0.3 mL, 1.2 mmol) in dioxane was added. The solution was stirred for 5 min at room temperature and then the solvent removed in vacuo. The residue was dissolved in MeOH (1 mL) and anhydrous Et₂O (20 mL) was added. The solid was collected by centrifuging. The title compound (100 mg, 41%) was afforded as a yellow solid. ¹H NMR (500 MHz, DMSO-d₆): δ 1.87-1.92 (m, 2H), 1.99-2.04 (m, 2H), 2.53 (s, 3H), 3.09-3.16 (m, 2H), 3.56-3.62 (m, 4H), 4.32 (t, J = 4.9 Hz, 2H), 7.00 (d, J = 9.2 Hz, 2H), 7.64 (t, J = 7.8 Hz, IH), 7.75 (d, J = 9.2 Hz, 2H), 8.03 (dd, J = 7.4, 0.8 Hz, IH), 8.31 (s, IH), 8.32 (dd, J = 8.0, 0.7 Hz, IH), 8.48 (s, IH), 9.58 (s, IH), 10.42 (br s, IH) MS (ES+): m/z 456 (M+H)⁺
EXAMPLE 55 Preparation of 2-(2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-5-
methylpyrimidin-4-yl)benzo[ b]thiophene-4-carbonitrile

[0254] To a solution of 15 (167 mg, 0.5 mmol) in dimethoxyethane (DME, 10 mL) was added a solution of 4-cyanobenzo[ b]thiophen-2-yl-2-boronic acid (117 mg, 0.55 mmol) in EtOH (5 mL), 2.0 M Na$_2$CO$_3$ (1.0 mL), and tetrakis(triphenylphosphine)palladium (0) (Pd(PPh$_3$)$_4$, 58 mg, 0.05 mmol). The reaction mixture was heated at 110 °C for 20 min under µ-wave. The hot solution was filtered and the solid washed with EtOAc. The organic solution was separated and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organic layer was dried (Na$_2$SO$_4$). The solvent was removed in vacuo. The crude product was purified by using HPLC. The HPLC fractions containing product were combined and neutralized with saturated NaHCO$_3$ (50 mL). The free base was extracted with EtOAc (2 x 100 mL). The organic layers were combined and dried (Na$_2$SO$_4$). The solvent was removed in vacuo. The residue was dissolved in MeOH (2 mL) and 4.0 M HCl solution (0.3 mL, 1.2 mmol) in dioxane was added. The solution was stirred for 5 min at room temperature and then the solvent removed in vacuo. The residue was dissolved in MeOH (1 mL) and anhydrous Et$_2$O (20 mL) was added. The solid was collected by centrifuging. The title compound (50 mg, 20%) was afforded as a brown solid. $^1$H NMR (500 MHz, DMSO-d$_6$): δ 1.87-1.92 (m, 2H), 1.99-2.04 (m, 2H), 2.55 (s, 3H), 3.08-3.15 (m, 2H), 3.55-3.62 (m, 2H), 4.34 (t, J = 5.0 Hz, 2H), 7.01 (d, J = 9.0 Hz, 2H), 7.63 (t, J = 7.8 Hz, IH), 7.76 (d, J = 9.0 Hz, 2H), 8.00 (d, J = 7.4 Hz, IH), 8.07 (s, IH), 8.45 (d, J = 8.4 Hz, IH), 8.50 (s, IH), 9.60 (s, IH), 10.84 (br s, IH) MS (ES+): m/z 456 (M+H)$^+$

EXAMPLE 56 Preparation of 5-{5-Methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-
phenylamino]-pyrimidin-4-yl}-thiophene-2-carbaldehyde (16)

[0255]
[0256] To a round bottomed flask was charged with 15 (1.0 g, 3.0 mmol), 5-formylthiophene-2-boronic acid (0.60 g, 3.9 mmol) and Pd(PPh$_3$)$_4$ (0.30 g, 0.26 mmol). DMF (10 mL) was added to the above mixture followed by aqueous sodium carbonate (2 M; 3.0 mL, 6.0 mmol). The reaction mixture was heated at 120 °C for 2 h. After cooling to room temperature, the mixture was filtered, the filtered solid washed with DCM and the filtrate concentrated. The crude product was purified by column chromatography on silica gel (DCM to 15% MeOH/DCM) to afford the title compound (0.30 g, 24%) as an orange solid.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.65-1.72 (m, 4H), 2.40 (s, 3H), 2.48-2.58 (m, 4H), 2.79 (t, $J$ = 5.6 Hz, 2H), 4.05 (t, $J$ = 5.9 Hz, 2H), 6.90 (d, $J$ = 9.1 Hz, 2H), 7.66 (d, $J$ = 9.1 Hz, 2H), 7.91 (d, $J$ = 4.0 Hz, IH), 8.10 (d, $J$ = 4.0 Hz, IH), 8.45 (s, IH), 9.46 (s, IH), 10.00 (s, IH)

MS (ES+): m/z 409 (M+H)$^+$

[0257] EXAMPLE 57 Preparation of 5-(5-{5-Methyl-2-[4-(2-pyrrolidin-l-yl-ethoxy)-phenylamino]-pyrimidin-4-yl }-thiophen-2-ylmethylene)-thiazolidine-2,4-dione

[0258] A microwave vial was charged with 16 (0.10 g, 0.25 mmol), thiazolidine-2,4-dione (45 mg, 0.39 mmol), and Cs$_2$CO$_3$ (0.12 g, 0.37 mmol) in a mixture of ethanol/DMF (4/1, 5 mL). The reaction mixture was heated for 30 min at 140 °C in a Biotage microwave reactor. The resulting reaction mixture was concentrated and the residue triturated in water. The resulting solid was filtered and purified by HPLC. The fractions were combined and poured into
saturated NaHCO₃ solution (30 mL). The combined aqueous layers were extracted with EtOAc (2 x 30 mL) and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue triturated in a mixture of EtOAc/hexanes (2/1, 15 mL). After filtration, the title compound was obtained as a reddish brown solid (20 mg, 16%).

¹H NMR (500 MHz, CDCl₃): δ 1.75-1.90 (m, 4H), 2.40 (s, 3H), 2.85-3.00 (m, 4H), 3.10-3.20 (m, 2H), 4.18 (t, J = 5.2 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 4.1 Hz, IH), 7.56 (s, IH), 7.75 (d, J = 4.0 Hz, IH), 7.78 (d, J = 9.0 Hz, 2H), 8.34 (s, IH), 9.39 (s, IH)

MS (ES+): m/z 508 (M+H)⁺

[0259] EXAMPLE 58 Enzyme Assays

[0260] The IC₅₀ values for compounds (shown below in Table 1) were determined using a luminescence-based kinase assay with recombinant JAK2, JAK3 and KDR (VEGF receptor) obtained from Invitrogen. In white, flat-bottom, 96-well plates (Nunc) parallel assays were run at room temperature at a final volume of 50 µL. Each well contained 40 µL of buffer consisting of 40 mM Tris buffer, pH 7.4, containing 50 mM MgCl₂, 800 µM EGTA, 350 µM Triton X-100, 2 mM β-mercaptoethanol, 250 µM peptide substrate and an appropriate amount of either JAK2, JAK3 or KDR (75 - 25 ng/well) such that the assay was linear over 60 min. The final concentrations of compounds for IC₅₀ value determinations ranged from 10 to 0.001 µM by adding the appropriate amount of compound in 2.5 µL of DMSO; the DMSO present in each assay was constant at 5%. The reaction was initiated by the addition of 10 µL of ATP to a final assay concentration of 3 µM. After the reaction had proceeded for 60 min, 50 µL of Kinase-Glo reagent (Promega) was added to terminate the reaction. This solution was then allowed to proceed for an additional 10 min to maximize the luminescence reaction. Values were then measured using an Ultra 384 instrument (Tecan) set for luminosity measurements.

Two control reactions were also run: one reaction containing no compound and the second containing neither inhibitor nor peptide substrate. IC₅₀ values were derived from experimental data using the non-linear curve fitting capabilities of Prism (Version 4; GraphPad Software). Results are reported in Table 1.

[0261] EXAMPLE 59 Cell Profileration Assay
The EC50 values for compounds (shown below in Table 1) were determined using a colormetric-based cell proliferation assay. In clear, flat-bottom, 96-well plates parallel assays were run at 37 °C and 6.5% CO2 at a final volume of 100 µL. Each well contained 99 µL of RPMI medium containing 10% inactivated fetal calf serum, 2 mM L-glutamine, 1 mM sodium pyruvate, non-essential amino acids and an appropriate amount of human erythroleukemia (HEL) cells that are driven by the V617F mutation of JAK2 and varying amounts of compound in DMSO. The final concentrations of compounds for EC50 value determinations ranged from 10 to 0.001 µM by adding the appropriate amount of compound in 1 µL of DMSO; the DMSO present in each assay was constant at 1%. The cells were allowed to proliferate in the presence of the inhibitor for approximately 72 h, XTT (3’-[l-(phenylamino-carbonyl)-3,4-tetrazolium]-bis(4-methoxy-6-nitro)benzene sulfonic acid) was added to a final concentration of 0.3 mg/mL. After the mixture was allowed to proceed for an additional 6 h, the absorbance values at 492 nm were measured to assess the formation of the formazan product. The absorbance at 690 nm was also measured for subtraction of turbidity values. EC50 values were derived from experimental data using the non-linear curve fitting capabilities of Prism (Version 4; GraphPad Software). Results reported in Table 1.

Table 1. Data for selected compounds against JAK2, JAK3, KDR in nM

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**[0264] EXAMPLE 6 0 TYK2 Enzyme Inhibition Study**

**[0265]** Inhibition of TYK2 by compounds of the invention was assessed using the Invitrogen single point method. The single point TYK2 inhibition data were obtained at a 250 nM concentration of test compound. A higher percent inhibition indicates a more potent compound in this assay. Each data point is the mean of two independent determinations. Inhibition levels of greater than >80% indicate virtually complete inhibition within the limits.
of experimental determination. For some compounds, IC$_{50}$ values were also determined. The results are given in Table 2.

Table 2: Data for selected compounds against TYK2

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<th>TYK2 IC$_{50}$ (nM)</th>
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<td><img src="image4" alt="Compound 42" /></td>
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<td>TYK2 IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
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<td>43</td>
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<td>TYK2 single point run at 250 nM compound</td>
<td>TYK2 IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
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<td>TYK2 IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
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Pharmacokinetic parameters were determined in mice following intravenous (IV) and oral (PO) doses. Male Balb/c mice were used (n=24 for IV and n=18 for PO, 3 animals/timepoint). Intravenous and oral dose formulations were prepared as needed. Dose was as follows: IV = 5 mg/kg, PO = 25 mg/kg. The time points for blood collection with IV dosing: 5, 15, 30 min, 1, 2, 4, 6, and 24 hr post dose (n=3 for each time-point). The time points for blood collection with PO dosing: 30 min, 1, 2, 4, 6, and 24 hr post dose (n=3 for each time-point).

Blood samples were collected by cardiac puncture. Blood was maintained in an ice and water mixture prior to centrifugation to obtain plasma. Plasma samples are transferred to a -20°C freezer and stored until analysis. Matrix calibration standards and QC samples were prepared by spiking the compound into blank mouse plasma. The final concentrations of a selected compound were 0, 1, 5, 10, 50, 100, 500, 1000, 2500 and 5000 ng/mL for calibration standards, and 2.50, 25.0, 250 and 2500 for QC samples.

Plasma samples were processed using a standard protocol. The samples were analyzed using a LC/MS/MS Waters Quattro LC by standard determined conditions. Chromatogram signals were integrated and calibrated using MassLynx 3.0. Pharmacokinetic parameters were estimated using WinNonlin (version 4.1) from mean plasma concentration-time profiles. The
values for the maximum plasma concentration ($C_{\text{max}}$) and the time to maximum concentration ($T_{\text{max}}$) were determined from measured plasma concentrations. The area under the curves, $\text{AUC}_{\text{last}}$ and $\text{AUC}_{\text{inf}}$ were calculated from plasma concentration-time profiles using the linear trapezoidal rule. The oral bioavailability ($F$) was calculated using the following equation;

$$F = \left( \frac{\text{AUQ}_0 - mf_{\text{po}} \times \text{Div}}{\text{AUC}_0 - 1_{\text{nf}} \times \text{D}_{\text{po}}} \right) \times 100\%.$$  

[0271] 4-(Benzo[b]thiophen-2-yl)-5-methyl-$N$-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine was tested following the above and gave $C_{\text{max}} = 1710 \text{ ng/mL}$, $T_{1/2} = 2.6 \text{ h}$, $V_{ss} = 5.5 \text{ L/kg}$, $CL = 50 \text{ niL/min/kg}$, and $\%F = 43\%$.

[0272] 4-[5-(3,5-Dimethyl-isoxazol-4-yl)-thiophen-2-yl]-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl] -amine was tested following the above and gave $C_{\text{max}} = 7670 \text{ ng/mL}$, $T_{1/2} = 5.1 \text{ h}$, $V_{ss} = 0.9 \text{ L/kg}$, $CL = 10 \text{ niL/min/kg}$, and $\%F = 31\%$.

[0273] As described above, mice were dosed orally (PO) with 25 mg/kg compound, and the plasma concentration at 1 and 4 hours was measured in triplicate. The results are given in Tables 3 and 4.

### Table 3: Plasma concentrations of compound 1 hour after dosing

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<th>Replicate#3</th>
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<td>181</td>
<td>195</td>
<td>14.5</td>
<td>7.4</td>
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</table>

### Table 4: Plasma concentrations of compound 4 hours after dosing

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<th>Replicate#2</th>
<th>Replicate#3</th>
<th>Mean</th>
<th>STDEV</th>
<th>%CV</th>
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</table>
[0276] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Equivalents

[0277] While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[0278] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention.
Claims

1. A compound represented by formula I:

\[
\begin{array}{c}
  & & R_1 \\
  & N & \\
 R_2 & & \text{I}
\end{array}
\]

wherein

- \( R_1 \) is a monocyclic or bicyclic heteroaryl containing at least one S atom, and is optionally substituted on a ring carbon by one or two substituents each independently selected from the group consisting of: halo, hydroxyl, nitro, formyl, cyano, formamido, carboxy, amino, amido, acylamino, carbamoyl, sulphanoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxycarbonyl, ureido, CF₃, N-alkylsulphanoyl, N,N-dialkylsulphanoyl, N-alkylcarbamoyl, -ORn, -OR₂Rn, -NRb-Rn, or -Ri₂Rn;

- \( R_2 \) is a phenyl or pyridinyl, wherein \( R_2 \) is optionally substituted on a ring carbon by one or two substituents each independently selected from the group consisting of: halo, hydroxyl, nitro, formyl, formamido, cyano, carboxy, amino, amido, acylamino, CF₃, carbamoyl, sulphanoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxycarbonyl, N-alkylsulphanoyl, N-alkylcarbamoyl, -ORn, -OR₂Rn, or -Ri₂Rn;

- \( R' \) is alkyl optionally substituted with one, two or three halogens;

- \( R_b \) is H or alkyl;

- \( R_n \) is independently selected for each occurrence, from the group consisting of: aryl, heteroaryl, cycloalkyl and heterocycloalkyl, wherein \( R_n \) can be optionally substituted by one to four substituents each independently selected from with halo, alkyl, carbonyl, halo, hydroxyl, nitro, formyl, formamido, cyano, carboxy, amino, amido, carbamoyl, sulphanoyl,
alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphanoyl, N,N-
dialkyl sulphonamoyl, N-alkyl carbamoyl, -O-alkylene-R_13, or -SO_2-R_13,

R_{12} is alkyiene, sulfonyl, carbonyl, or a bond;

R_{i4} is alkyiene, alkenylene, sulfonyl, or a bond;

R_{i3} is independently selected from the group consisting of: aryl, heteroaryl, cycloalkyl
and heterocycloalkyl, wherein R_{i3} can be optionally substituted by one to four substituents
each independently selected from the group consisting of: halo, alkyl, carbonyl, hydroxyl,
nitro, formyl, formamido, carboxy, cyano, amino, amido, carbamoyl, sulphanoyl, alkyl,
alkenyl, alkylnyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkysulphanoyl, N,N-
dialkyl sulphonamoyl, N-alkyl carbamoyl; or

pharmaceutically acceptable salts or N-oxides thereof.

2. The compound of claim 1, wherein R_{i} is an optionally substituted monocyclic or bicyclic
heteroaryl, optionally substituted by one or two substituents each independently selected from
the group consisting of alkyl, wherein said alkyl is optionally substituted by one or two
moieties selected from halo, hydroxyl, or cyano.

3. The compound of claim 2, wherein said alkyl is chosen from methyl, ethyl, or propyl.

4. The compound of claim 1 or 2, wherein R_{i} is selected from the group consisting of:
optionally substituted thiophene or optionally substituted benzothiophene.

5. The compound of any one of claims 1-4, wherein R’ is methyl.

6. The compound of any one of claims 1-5 wherein R_{1} is represented by:

\[
\begin{array}{c}
\text{R}_{3} \\
\text{S} \\
\text{R}_{4}
\end{array}
\]
wherein $R_3$ and $R_4$ may each be independently selected from the group consisting of: hydrogen, halo, hydroxyl, nitro, formyl, formamido, carboxy, amino, carbamoyl, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphamoyl, N-alkyl carbamoyl, $\text{-OR}_1$, $\text{-OR}_{1\text{r}}$, $\text{-N}\text{R}_1\text{R}_{1\text{r}}$, or $\text{-R}_1\text{R}_{1\text{r}}$, or $R_3$ and $R_4$ taken together with the carbon atoms to which they are attached form a 5 or 6 membered carbocyclic or heterocyclic ring, optionally substituted by one to two substituents each independently selected from the group consisting of: halo, alkyl, carbonyl, hydroxyl, nitro, formyl, formamido, carboxy, amino, carbamoyl, sulphamoyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphamoyl, N,N-dialkyl sulphamoyl, and N-alkyl carbamoyl.

7. The compound of any one of claims 1-6 wherein $R_1$ is selected from:

![](image1)

and

wherein for each occurrence, $R_5$ is independently selected from the group consisting of: hydrogen, halo, hydroxyl, nitro, formyl, formamido, carboxy, amino, amido, acylamino, cyano, carbamoyl, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphamoyl, N-alkyl carbamoyl, $\text{-R}_{1\text{r}}$, or $\text{-R}_{1\text{r}}\text{R}_{1\text{r}}$; and $R_5'$ is selected from the group consisting of: H, alkyl, sulphonyl, and carbonyl.

8. The compound of any one of claims 1-7 wherein $R_2$ is

![](image2)

wherein:
X is N or CR₈;

R₇ and R₈, independently for each occurrence, is chosen from the group consisting of:
H, heterocycle, heteroaryl, -O-alkylene-heterocycle or -O-heteroaryl, wherein said heterocycle
or heteroaryl is optionally substituted with one to three substituents each independently
selected from the group consisting of: halo, alkyl, carbonyl, cyano, CF₃, hydroxyl, nitro,
formyl, formamido, carboxy, amino, carbamoyl, sulphamoyl, alkenyl, alkynyl, alkoxy,
alkanoyl, alkoxy carbonyl, N-alkylsulphamoyl, N,N-dialkylsulphamoyl and N-alkyl carbamoyl,
and wherein at least one R₈ is H.

9. The compound of claim 8, wherein R₇ is a heterocycle or a methyl-substituted heterocycle.

10. The compound of claim 8, wherein R₈ is H and R₇ is a heterocycle, or -O-alkylene-
heterocycle, wherein said heterocycle is chosen from the group consisting of: pyrrolidinyl,
piperazinyl, piperidinyl, or morpholinyl.

11. The compound of claim 8, where ine each R₈ is H and R₇ is an optionally substituted
imidazole.

12. The compound of claim 8, wherein each R₈ is H and R₇ is selected from the group
consisting of: methylpiperazine, piperazine, N-(4-(2-methyl-lH-imidazol-l-yl), imidazole, or
2-pyrrolidin- lylethoxy.

13. The compound of any one of claims 8-12, wherein X is C.

14. A compound represented by formula II or formula III:
wherein:

R₃ and R₄ may each be independently selected from the group consisting of: hydrogen, halo, hydroxyl, nitro, formyl, formamido, carboxy, cyano, amino, amido, acylamido, carbamoyl, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphamoyl, N,N-dialkyl sulphamoyl, N-alkyl carbamoyl, \(-\text{OR}_{11}, -\text{NRbR}_{11}, \text{or } -\text{R}_{11}^\prime \text{R}_{11}^\prime\);

R₉ is independently selected from the group consisting of: hydrogen, halo, hydroxyl, nitro, formyl, formamido, carboxy, amino, amido, acylamino, cyano, carbamoyl, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphamoyl, or N-alkyl carbamoyl;

X is N or CR₉;

R₇ and R₈ are each independently chosen from H, \(-\text{R}_{12} \text{R}_{13}, \text{or } -\text{OR}_{12} \text{R}_{13}\) wherein at least one R₈ is H;

R₉ is H or alkyl;

Rₙ is independently selected from the group consisting of: aryl, heteroaryl, cycloalkyl and heterocycloalkyl, wherein R₁₁ can be optionally substituted by one to four substituents each independently selected from the group consisting of: halo, alkyl, carbonyl, halo, hydroxyl, nitro, formyl, formamido, cyano, carboxy, amino, amido, acylamino, carbamoyl, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphamoyl, N,N-dialkyl sulphamoyl, N-alkyl carbamoyl, \(-\text{O-alkylene-R}_{13}, \text{R}_{13} \text{or } -\text{SO}_{2}-\text{R}_{13}\);

R₁₃ is independently selected from the group consisting of: aryl, cycloalkyl, heteroaryl or heterocycloalkyl, each optionally substituted by one to four substituents each independently selected from the group consisting of: halo, alkyl, carbonyl, hydroxyl, nitro, formyl, formamido, carboxy, cyano, amino, amido, acylamino, carbamoyl, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkyl sulphamoyl, N,N-dialkyl sulphamoyl, or N-alkyl carbamoyl,

R₁₂ is chosen from: alkylene or a bond;
R is chosen from: alkylene, alkenylene, -SO₂-, or a bond; and pharmaceutically acceptable salts and N-oxides thereof.

15. The compound of claim 14, wherein R₁ is H.

16. The compound of claims 14 or 15, wherein R₄ is selected from the group consisting of: H, halo, cyano, carboxyl, alkyl, heteroaryl each optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of: halo, hydroxyl, alkyl or branched alkyl, -NH-phenyl or -phenyl, wherein said phenyl is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of: N-alkylsulphamoyl, heterocycle, -S(O)₂-heterocycle, straight chain alkyl, branched alkyl, or -O-alkylene-heterocycle.

17. The compound of claim 16, wherein said alkyl is chosen from methyl, ethyl, or propyl.

18. The compound of claim 14, wherein R₉ is H.

19. The compound of claim 14, wherein at least one R₉ is alkyl.

20. The compound of claim 19, wherein at least one R₉ is methyl.

21. The compound of any one of claims 14-20, wherein R₇ or R₈ is selected from the group consisting of:
22. The compound of any one of claims 14-21, wherein \( R_3 \) is H and \( R_4 \) is selected from the group consisting of:
23. A compound selected from the group consisting of: (5-Methyl-4-thiophen-2-yl-pyrimidin-2-yl)-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; (5-Methyl-4-thiophen-2-yl-pyrimidin-2-yl)-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; (5-Methyl-4-thiophen-2-yl-pyrimidin-2-yl)-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; (5-Methyl-4-thiophen-2-yl-pyrimidin-2-yl)-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine;
yl)-phenyl-amine; (5-Methyl-4-thiophen-2-yl-pyrimidin-2-yl)-pyridin-3-yl-amine; [5-Methyl-4-(5-phenyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(4-methyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(3-methyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(5-methyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(4-methyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(3-methyl-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(5-chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-(5-chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-(5-Chloro-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl]-thiophen-2-yl]-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-(5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl)-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol; N-Methyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-yl)-methanol;
(mopholine-4-sulfonyl)-phenyl)-thiophen-2-yl]-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-(5-phenylamino-thiophen-2-yl)-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-[5-(3-piperazin-1-yl-phenyl)-thiophen-2-yl]-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [4-(5-Isoxazol-4-yl-thiophen-2-yl)-5-methyl-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; [5-Methyl-4-[5-(3-piperazin-1-yl-phenyl)-thiophen-2-yl]-pyrimidin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine; iV-tert-Butyl-3-(5-{5-methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-ylamino)-benzenesulfonamide; 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine; iV-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenyl)-4-(benzo[b]thiophen-2-yl)-5-methylpyrimidin-2-amine; 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(4-(piperidin-4-yloxy)phenyl)pyrimidin-2-amine; 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(3-(piperazin-1-yl)phenyl)pyrimidin-2-amine; 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(6-(piperazin-1-yl)pyridin-3-yl)pyrimidin-2-amine; 4-(Benzo[b]thiophen-2-yl)-5-methyl-N-(4-(2-methyl-1H-imidazol-1-yl)phenyl) pyrimidin-2-amine; 5-Methyl-4-(5-methylbenzo[b]thiophen-2-yl)-N-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-yl)benzo[b]thiophene-6-carbonitrile; 2-(2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-yl)benzo[b]thiophene-7-carbonitrile; 2-(2-(4-(2-(Pyrrolidin-1-yl)ethoxy)phenylamino)-5-methylpyrimidin-4-yl)benzo[b]thiophene-4-carbonitrile; 5-(5-{5-Methyl-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-thiophen-2-ylmethylene)-thiazolidine-2,4-dione; N-fert-butyl-3-(5-(5-methyl-2-(4-(piperidin-1-ylmethyl)phenylamino)pyrimidin-4-yl)thiophen-2-
yl)benzenesulfonamide; 4-(5-(3,5-diethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(2-
pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3,5-dimethylisoxazol-4-yl)thiophen-
2-yl)-5-methyl-N-(3-(morpholinomethyl)phenyl)pyrimidin-2-amine; N-(4-(2-(pyrrolidin-1-
yl)ethoxy)phenyl)-4-(thiophen-2-yl)pyrimidin-2-amine; 4-(3-methylthiophen-2-yl)-N-(4-(2-
(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; (Z)-5-((5-(5-methyl-2-(4-(2-(pyrrolidin-
1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)methylene)imidazolidine-2,4-dione; A-
(5-(benzo[d][1,3]dioxol-5-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-
yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)thiophen-2-
yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 2-(5-methyl-2-(4-(4-
 methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)benzo[b]thiophene-4-carbonitrile; N-tert-
butyl-3-(5-(5-methyl-2-(4-(piperidin-1-ylmethyl)phenylamino)pyrimidin-4-yl)thiophen-2-
yl)benzenesulfonamide; 4-(5-(3,5-diethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(2-
(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3,5-dimethylisoxazol-4-yl)thiophen-
2-yl)-5-methyl-N-(3-(morpholinomethyl)phenyl)pyrimidin-2-amine; N-tert-butyl-3-(5-(5-
methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)thiophen-2-
yl)benzenesulfonamide; 4-(5-(3,5-diethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-
(piperidin-1-ylmethyl)phenyl)pyrimidin-2-amine; N-tert-butyl-2-(5-(5-methyl-2-(4-(2-
(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzenesulfonamide; 4-(5-
(2,6-dimethylphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-
yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(2,6-dimethoxyphenyl)thiophen-2-yl)-5-methyl-N-
(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(2-isopropoxy-6-
methoxyphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-
amine; 4-(5-(2-isopropylphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-
yl)ethoxy)phenyl)pyrimidin-2-amine; N-isopropyl-3-(5-(5-methyl-2-(4-(2-(pyrrolidin-1-

- 130 -
(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzenesulfonamide; N,N-diethyl-3-(5-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzenesulfonamide; 4-(5-(3-isopropylphenyl)thiophen-2-yl)-5-methyl-N-(4-(morpholinomethyl)phenyl)pyrimidin-2-amine; 4-(5-(3-isopropylphenyl)thiophen-2-yl)-5-methyl-N-(4-(piperidin-1-ylmethyl)phenyl)pyrimidin-2-amine; 4-(5-(3-isopropoxyphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3-isopropoxyphenyl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; N-cyclopropyl-3-(5-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzamide; 5-methyl-4-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzenesulfonamide; N,N-diethyl-3-(5-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzamide; (3-(5-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)phenyl)(4-methylpiperazin-1-yl)methanone; N-tert-butyl-3-(5-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzamide; 5-methyl-4-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)thiophen-2-yl)benzamide;
phenylthiophen-2-yl)-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(4-(3,5-dimethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3,5-dimethyl-lH-pyrazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-4-(5-(1,3,5-trimethyl-lH-pyrazol-4-yl)thiophen-2-yl)pyrimidin-2-amine; 4-(5-(3,5-dimethylisoxazol-4-yl)benzo[b]thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 2-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)benzo[b]thiophene-5-carbonitrile; 5-methyl-4-(5-(methylsulfbnyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 2,2-dimethyl-1-(2-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one; 1-(2-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)benzo[b]thiophen-5-yl)pentan-1-one; 4-(5-(5-tert-butyl-1,2,4-oxadiazol-3-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(5-butyl-5-(morpholinomethyl)-2,5-dihydro-1,2,4-oxadiazol-3-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(5-tert-butyl-1,2,4-oxadiazol-3-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(5-tert-butyl-1,2,4-oxadiazol-3-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(5-isopropyl-1,2,4-oxadiazol-3-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(3,5-dimethyl-1H-pyrazol-4-yl)thiophen-2-yl)-5-methyl-N-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)pyrimidin-2-amine; 4-(5-(2-methyl-1H-imidazol-1-yl)methyl)phenyl)pyrimidin-2-amine; 2-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yl)benzo[b]thiophen-5-
yl)(morpholino)methanone; 4-(5-(3,5-dimethylisoxazol-4-yl)thiophen-2-yl)-5-methyl-N-(3-(4-
methylpiperazin-1-yl)phenyl)pyrimidin-2-amine; 3-methyl-5-(5-methyl-2-(3-(4-
methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)thiophene-2-carbonitrile; 3-methyl-5-(5-
methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)thiophene-2-carbonitrile;
(2-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)benzo[b]thiophen-5-
yl)(morpholino)methanone; 5-methyl-N-(3-(4-methylpiperazin-1-yl)phenyl)-4-(4,5,6,7-
tetrahydrothieno[3,2-c]pyridin-2-yl)pyrimidin-2-amine; N,N-diethyl-2-(5-methyl-2-(3-(4-
methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-
carboxamide; 5-methyl-N-(3-(4-methylpiperazin-1-yl)phenyl)-4-(5-(methylsulfonyl)-4,5,6,7-
tetrahydrothieno[3,2-c]pyridin-2-yl)pyrimidin-2-amine; 1-(2-(5-methyl-2-(3-(4-
methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-
yl)ethanone; 2-methyl-1-(2-(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-
yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one; (2-(5-methyl-2-(3-(4-
methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-
yl)(morpholino)methanone; N-tert-butyl-2-(5-methyl-2-(3-(4-methylpiperazin-1-
yl)phenylamino)pyrimidin-4-yl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide; and (2-
(5-methyl-2-(3-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yl)benzo[b]thiophen-5-
yl)(piperidin-1-yl)ethanone;
or pharmaceutically acceptable salts and N-oxides thereof.

24. The compound of any one of claims 1-23, wherein said compound inhibits signaling
through any of Jak kinases.

25. The compound of any one of claims 1-24, wherein said compound inhibits one or more of:
JAK1, JAK2, JAK3, and TYK2.
26. The compound of any one of claims 1-25, wherein said compound does not substantially 
modulate KDR.

27. A method for treating a myeloproliferative disorder in a patient in need thereof, 
comprising administering an effective amount of a compound of any one of claims 1-23.

28. The method of claim 27, wherein the myeloproliferative disorder is one of: polycythemia 
vera, myelofibrosis, and essential thrombocytemia.

29. A method for treating polycythemia vera in a patient in need thereof, comprising 
administering an effective amount of a compound of any one of claims 1-23.

30. A method for treating myelofibrosis in a patient in need thereof, comprising administering 
an effective amount of a compound of any one of claims 1-23.

31. A method for treating essential thrombocytemia in a patient in need thereof, comprising 
administering an effective amount of a compound of any one of claims 1-23.

32. A method for treating acute myeloid leukemia (AML) in a patient in need thereof, 
comprising administering an effective amount of a compound of any one of claims 1-23.

33. A method of treating cancer in a patient in need thereof, comprising administering an 
effective amount of a compound of any one of claims 1-23.

34. A method of treating an immune disorder and/or inflammation in a patient in need 
thereof, comprising administering an effective amount of a compound of any one of claims 1-
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35. A method of treating respiratory inflammation in a patient in need thereof, comprising 
administering an effective amount of a compound of any one of claims 1-23.

36. A method of treating asthma in a patient in need thereof, comprising administering an 
effective amount of a compound of any one of claims 1-23.
37. A method of treating chronic obstructive pulmonary disease (COPD) in a patient in need thereof, comprising administering an effective amount of a compound of any one of claims 1-23.

38. A method of rheumatoid arthritis (RA) in a patient in need thereof, comprising administering an effective amount of a compound of any one of claims 1-23.

39. A method of treating rheumatoid arthritis (RA), psoriatic arthritis, asthma, COPD, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, type I diabetes mellitus, myasthenia gravis, thyroiditis, myocarditis, psoriasis, immunoglobulin nephropathies, uveitis, iritis, scleritis, conjunctivitis, graft versus host disease, multiple myeloma, prostrate cancer, systemic lupus erythematosus, or dermatitis in a patient in need thereof, comprising administering an effective amount of a compound of any one of claims 1-23.

40. A method of treating age related macular degeneration, diabetic macular edema, and/or proliferative diabetic retinopathy, comprising administering an effective amount of a compound of any one of claims 1-23.

41. A composition comprising a compound of any one of claims 1-23 and a pharmaceutically acceptable excipient.

42. The compound of any one of claims 1-13 and Formula I, wherein when R’ is methyl, the compound inhibits JAK2 or TYK2 with an IC₅₀ at least about ten times lower as compared to a compound represented by Formula I when R’ is H, and R₁, R₂, R₃, R₄ and R₅ are as defined in any one of claims 1-13.

43. A process for forming a compound of Formula I:

   \[
   \begin{array}{c}
   \text{R}^1 \quad \text{R}^2 \\
   \text{N} \quad \text{N} \\
   \text{R}^1 \quad \text{R}^2
   \end{array}
   \]

   wherein

   R₁ is an monocyclic or bicyclic heteroaryl containing least one S atom, and is optionally substituted on a ring carbon by one or two substituents each independently selected.
from the group consisting of: halo, hydroxyl, nitro, formyl, cyano, formamido, carboxy,
amino, amido, acylamino, carbamoyl, sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl,
alkoxycarbonyl, ureido, CF₃, N-alkylsulphamoyl, N,N-dialkylsulphamoyl, N-alkylcarbamoyl,
ORn, -ORi₂Rn, -NRb-Rn, or -Ri₄Rn;

R₂ is a phenyl or pyridinyl, wherein R₂ is optionally substituted on a ring carbon by one
or two substituents each independently selected from the group consisting of: halo, hydroxyl,
nitro, formyl, formamido, cyano, carboxy, amino, amido, acylamino, CF₃, carbamoyl,
sulphamoyl, alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkylsulphamoyl, N-
alanyl carbamoyl, -ORn, -ORi₂Rn, or -Ri₂Rn;

R’ is alkyl optionally substituted with one, two or three halogens;

Rb is H or alkyl;

Rn is independently selected for each occurrence, from the group consisting of: aryl,
heteroaryl, cycloalkyl and heterocycloalkyl, wherein Rn can be optionally substituted by one
to four substituents each independently selected from with halo, alkyl, carbonyl, halo,
hydroxyl, nitro, formyl, formamido, cyano, carboxy, amino, amido, carbamoyl, sulphamoyl,
alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkylsulphamoyl, N,N-
dialkylsulphamoyl, N-alkylcarbamoyl, -O-alkylene-Ri₃, Ri₃; or -SO₂-Ri₃,

Ri₂ is alkylene, sulfonyl, carbonyl, or a bond;

Ri₄ is alkylene, alkenylene, sulfonyl, or a bond;

Ri₃ is independently selected from the group consisting of: aryl, heteroaryl, cycloalkyl
and heterocycloalkyl, wherein Ri₃ can be optionally substituted by one to four substituents
each independently selected from the group consisting of: halo, alkyl, carbonyl, hydroxyl,
nitro, formyl, formamido, carboxy, cyano, amino, amido, carbamoyl, sulphamoyl, alkyl,
alkenyl, alkynyl, alkoxy, alkanoyl, alkoxy carbonyl, N-alkylsulphamoyl, N,N-
dialkylsulphamoyl, N-alkylcarbamoyl; or pharmaceutically acceptable salts or N-oxides
thereof,

comprising reacting a compound of formula IV:
wherein $Y$ is a boronic acid or halogen, with $R_2\text{-NH}_2$ to obtain the compound of Formula I.
INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/078932

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D409/04 C07D409/14 C07D413/14 C07D417/14 A61K31/506

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

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, BEILSTEIN Data, CHEMABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C

See patent family annex

* Special categories of cited documents
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'E' earlier document but published on or after the international filing date
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'A' document member of the same patent family

Date of the actual completion of the international search: 21 January 2009

Date of mailing of the international search report: 03/02/2009

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) 340-3516

Authorized officer
Herz, Claus
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