Title: CHEMICAL COMPOUNDS

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(57) Abstract: The present invention relates to compounds of Formula (I): and to their salts, pharmaceutical compositions, methods of use, and methods for their preparation. These compounds provide a treatment for myeloproliferative disorders and cancer.  

\[
\text{\begin{align*}
\text{R}^1 & \equiv \text{H, CH}_{3}
\text{R}^2 & \equiv \text{H, CH}_{3}
\text{R}^3 & \equiv \text{H, CH}_{3}
\end{align*}}
\]

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Chemical Compounds

Field of the Invention

The present invention relates to novel compounds, their pharmaceutical compositions and methods of use. In addition, the present invention relates to therapeutic methods for the treatment and prevention of cancers and to the use of these compounds in the manufacture of medicaments for the treatment and prevention of myeloproliferative disorders and cancers.

Background of the Invention

The JAK (Janus-associated kinase)/STAT (signal transducers and activators of transcription) signalling pathway is involved in a variety of hyperproliferative and cancer related processes including cell-cycle progression, apoptosis, angiogenesis, invasion, metastasis and evasion of the immune system (Haura et al., Nature Clinical Practice Oncology, 2005, 2(6), 315-324; Verna et al., Cancer and Metastasis Reviews, 2003, 22, 423-434).

The JAK family consists of four non-receptor tyrosine kinases Tyk2, JAK1, JAK2, and JAK3, which play a critical role in cytokine- and growth factor mediated signal transduction. Cytokine and/or growth factor binding to cell-surface receptor(s), promotes receptor dimerization and facilitates activation of receptor-associated JAK by autophosphorylation. Activated JAK phosphorylates the receptor, creating docking sites for SH2 domain-containing signalling proteins, in particular the STAT family of proteins (STAT1, 2, 3, 4, 5a, 5b and 6). Receptor-bound STATs are themselves phosphorylated by JAKs, promoting their dissociation from the receptor, and subsequent dimerization and translocation to the nucleus. Once in the nucleus, the STATs bind DNA and cooperate with other transcription factors to regulate expression of a number of genes including, but not limited to, genes encoding apoptosis inhibitors (e.g. Bcl-XL, Mcl-I) and cell cycle regulators (e.g. Cyclin D1/D2, c-myc) (Haura et al., Nature Clinical Practice Oncology, 2005, 2(6), 315-324; Verna et al., Cancer and Metastasis Reviews, 2003, 22, 423-434).

Over the past decade, a considerable amount of scientific literature linking constitutive JAK and/or STAT signalling with hyperproliferative disorders and cancer has been published.
Constitutive activation of the STAT family, in particular STAT3 and STAT5, has been detected in a wide range of cancers and hyperproliferative disorders (Haura et al., Nature Clinical Practice Oncology, 2005, 2(6), 315-324). Furthermore, aberrant activation of the JAK/STAT pathway provides an important proliferative and/or anti-apoptotic drive downstream of many kinases (e.g. Flt3, EGFR) whose constitutive activation have been implicated as key drivers in a variety of cancers and hyperproliferative disorders (Tibes et al., Annu Rev Pharmacol Toxicol 2550, 45, 357-384; Choudhary et al., International Journal of Hematology 2005, 82(2), 93-99; Sordella et al., Science 2004, 305, 1163-1167). In addition, impairment of negative regulatory proteins, such as the suppressors of cytokine signalling (SOCS) proteins, can also influence the activation status of the JAK/STAT signalling pathway in disease (JC Tan and Rabkin R, Pediatric Nephrology 2005, 20, 567-575).

Several mutated forms of JAK2 have been identified in a variety of disease settings. For example, translocations resulting in the fusion of the JAK2 kinase domain with an oligomerization domain, TEL-JAK2, Bcr-JAK2 and PCM1-JAK2, have been implicated in the pathogenesis of various hematologic malignancies (SD Turner and Alesander DR, Leukemia, 2006, 20, 572-582). More recently, a unique acquired mutation encoding a valine-to-phenylalanine (V617F) substitution in JAK2 was detected in a significant number of polycythemia vera, essential thrombocytemia and idiopathic myelofibrosis patients and to a lesser extent in several other diseases. The mutant JAK2 protein is able to activate downstream signalling in the absence of cytokine stimulation, resulting in autonomous growth and/or hypersensitivity to cytokines and is believed to play a role in driving these diseases (MJ Percy and McMullin MF, Hematological Oncology 2005, 23(3-4), 91-93).

**Summary of the Invention**

The present invention relates to compounds of Formula (I):
The compounds of Formula (I) are believed to possess JAK kinase inhibitory activity and are accordingly useful for their anti-proliferation and/or pro-apoptotic activity and in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said compound, or pharmaceutically acceptable salts thereof, to pharmaceutical compositions containing it and to its use in the manufacture of medicaments for use in the production of an anti-proliferation and/or pro-apoptotic effect in warm-blooded animals such as man. Also in accordance with the present invention the applicants provide methods of using said compound, or pharmaceutically acceptable salts thereof, in the treatment of myeloproliferative disorders, myelodysplastic syndrome and cancer.

The properties of the compounds of Formula (I) are expected to be of value in the treatment of myeloproliferative disorders, myelodysplastic syndrome, and cancer by inhibiting the tyrosine kinases, particularly the JAK family and more particularly JAK2. Methods of treatment target tyrosine kinase activity, particularly the JAK family activity and more particularly JAK2 activity, which is involved in a variety of myeloproliferative disorders, myelodysplastic syndrome and cancer related processes. Thus, inhibitors of tyrosine kinases, particularly the JAK family and more particularly JAK2, are expected to be active against myeloproliferative disorders such as chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myeloid metaplasia with myelofibrosis, idiopathic myelofibrosis, chronic myelomonocytic leukemia and
hypereosinophilic syndrome, myelodysplastic syndromes and neoplastic disease such as carcinoma of the breast, ovary, lung, colon, prostate or other tissues, as well as leukemias, myelomas and lymphomas, tumors of the central and peripheral nervous system, and other tumor types such as melanoma, fibrosarcoma and osteosarcoma. Tyrosine kinase inhibitors, particularly the JAK family inhibitors and more particularly JAK2 inhibitors are also expected to be useful for the treatment other proliferative diseases including but not limited to autoimmune, inflammatory, neurological, and cardiovascular diseases.

Furthermore, the compounds of Formula (I), or pharmaceutically acceptable salts thereof, are expected to be of value in the treatment or prophylaxis of against myeloproliferative disorders selected from chronic myeloid leukemia, polycytemia vera, essential thrombocytemia, myeloid metaplasia with myelofibrosis, idiopathic myelofibrosis, chronic myelomonocytic leukemia and hypereosinophilic syndrome, myelodysplastic syndromes and cancers selected from oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, Ewings sarcoma, neuroblastoma, Kaposi's sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, mesothelioma, renal cancer, lymphoma and leukaemia; particularly myeloma, leukemia, ovarian cancer, breast cancer and prostate cancer.

**Detailed Description of the Invention**

The present invention relates to compounds of Formula (I):

![Formula (I)]
or pharmaceutically acceptable salts thereof, wherein

Ring A is selected from pyridinyl and pyrimidinyl;

R\(^1\) is halo;

\[ R^2 \] is selected from methyl, C\(_2\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, carbocyclyl, heterocyclyl, -OR\(^2a\), -SR\(^2a\), -N(R\(^2a\))_2, -N(R\(^2a\))C(O)R\(^2b\), -N(R\(^2a\))N(R\(^2a\))_2, -NO\(_2\), -N(R\(^2a\))OR\(^2a\), -ON(R\(^2a\))_2, -C(O)H, -C(O)R\(^2b\), -C(O)\(_2\)R\(^2b\), -C(O)N(R\(^2a\))_2, -C(O)N(R\(^2a\))(OR\(^2a\)) -OC(O)N(R\(^2a\))_2, -N(R\(^2a\))C(O)\(_2\)R\(^2a\), -N(R\(^2a\))C(O)N(R\(^2a\))_2, -OC(O)R\(^2b\), -S(O)R\(^2b\), -S(O)\(_2\)R\(^2b\), -S(O)\(_2\)N(R\(^2a\))_2, -N(R\(^2a\))S(O)\(_2\)R\(^2b\), -C(R\(^2a\))=N(R\(^2a\)), and -C(R\(^2a\))=N(OR\(^2a\)), wherein said methyl is substituted with at least one R\(^{20}\),

wherein said C\(_2\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, carbocyclyl, and heterocyclyl are optionally substituted on carbon with one or more R\(^{20}\), and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R\(^{20*}\);

R\(^{20}\) in each occurrence is independently selected from Ci-alkyl, carbocyclyl, heterocyclyl, -C(O)H, -C(O)R\(^{2b}\), -C(O)\(_2\)R\(^{2c}\), -C(O)N(R\(^{2a}\))_2, -S(O)R\(^{2b}\), -S(O)\(_2\)R\(^{2b}\), -S(O)\(_2\)N(R\(^{2a}\))_2, -C(R\(^{2a}\))=N(R\(^{2a}\)), and -C(R\(^{2a}\))=N(OR\(^{2a}\)), wherein said Ci-alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R\(^{20}\), and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R\(^{20*}\);

R\(^{2a}\) in each occurrence is independently selected from H, Ci-alkyl, carbocyclyl, and heterocyclyl, wherein said Ci-alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R\(^{20}\), and wherein any -NH-moiety of said heterocyclyl is optionally substituted with R\(^{20*}\);

R\(^{2b}\) in each occurrence is independently selected from Ci-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, carbocyclyl, and heterocyclyl, wherein said Ci-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R\(^{20}\), and wherein any -NH-moiety of said heterocyclyl is optionally substituted with R\(^{20*}\);

R\(^{2c}\) in each occurrence is independently selected from Ci-alkyl, carbocyclyl, and heterocyclyl, wherein said Ci-alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R\(^{20}\), and wherein any -NH-moiety of said heterocyclyl is optionally substituted with R\(^{20*}\);

R\(^3\) is halo;
R in each occurrence is independently selected from halo, -CN, Ci-alkyl, C₂-alkenyl, C₂-alkynyl, carbocyclyl, heterocyclyl, -OR, -SR, -N(R₂), -N(R₂)C(O)R, -N(R₂)N(R₂), -NO₂, -N(R₂), -O-N(R₂), -C(O)H, -C(O)R, -C(O)₂R, -C(O)N(R₂), -C(O)₂N(R₂), -OC(O)R, -S(O)R, -S(O)₂R, -S(O)₂N(R₂), -N(R₂)S(O)₂R, -C(R₂)=N(R₂), and -C(R₂)=N(OR₂);  

R in each occurrence is independently selected from Ci-alkyl, carbocyclyl, heterocyclyl, -C(O)H, -C(O)R, -C(O)₂R, -C(O)N(R₂), -S(O)R, -S(O)₂R, -S(O)₂N(R₂), -C(R₂)=N(R₂), and -C(R₂)=N(OR₂);  

R in each occurrence is independently selected from H, Ci-alkyl, carbocyclyl, and heterocyclyl;  

R in each occurrence is independently selected from Ci-alkyl, C₂-alkenyl, C₂-alkynyl, carbocyclyl, and heterocyclyl;  

R in each occurrence is independently selected from Ci-alkyl, carbocyclyl, and heterocyclyl;  

and  
n is 1 or 2.

In this specification the prefix Cₓᵧ as used in terms such as Cₓᵧ-alkyl and the like (where x and y are integers) indicates the numerical range of carbon atoms that are present in the group; for example, Ci-alkyl includes Calkyl (methyl), C₂alkyl (ethyl), C₃alkyl (propyl and isopropyl) and C₄alkyl (butyl, 1-methylpropyl, 2-methylpropyl, and tert-butyl).

**Alkyl** - As used herein the term "alkyl" refers to both straight and branched chain saturated hydrocarbon radicals having the specified number of carbon atoms. References to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only.

**Alkenyl** - As used herein, the term "alkenyl" refers to both straight and branched chain hydrocarbon radicals having the specified number of carbon atoms and containing at least one carbon-carbon double bond. For example, "C₂-alkenyl" includes, but is not limited to, groups
such as C2-6alkenyl, C2-4alkenyl, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, and 5-hexenyl.

Alkynyl - As used herein, the term "alkynyl" refers to both straight and branched chain hydrocarbon radicals having the specified number of carbon atoms and containing at least one carbon-carbon triple bond. For example, "C2-6alkynyl" includes, but is not limited to, groups such as C2-6alkynyl, C2-4alkynyl, ethynyl, 2-propynyl, 2-methyl-2-propynyl, 3-butylnyl, 4-pentynyl, and 5-hexynyl.

Halo - As used herein, the term "halo" refers to fluoro, chloro, bromo and iodo. In one aspect, the term "halo" may refer to fluoro, chloro, and bromo. In another aspect, the term "halo" may refer to fluoro and chloro.

Carbocyclyl - As used herein, the term "carbocyclyl" refers to a saturated, partially saturated, or unsaturated, mono or bicyclic carbon ring that contains 3 to 12 ring atoms, of which one or more -CH$_2$- groups may be optionally replaced with a corresponding number of -C(O)- groups. Illustrative examples of "carbocyclyl" include, but are not limited to, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, indanyl, naphthyl, oxocyclopentyl, 1-oxoindanyl, phenyl, and tetralinyl. In one aspect, "carbocyclyl" may refer to cyclopropyl.

3- to 6-Membered Carbocyclyl - In one aspect, "carbocyclyl" may be 3- to 6-membered carbocyclyl. The term "3- to 6-membered carbocyclyl" refers to a saturated or partially saturated monocyclic carbon ring containing 3 to 6 ring atoms, of which one or more -CH$_2$- groups may be optionally replaced with a corresponding number of -C(O)- groups. Illustrative examples of "3- to 6-membered carbocyclyl" include cyclopropyl, cyclobutyl, cyclopentyl, oxocyclopentyl, cyclopentenyl, cyclohexyl, and phenyl.

Heterocyclyl - As used herein, the term "heterocyclyl" refers to a saturated, partially saturated, or unsaturated, mono or bicyclic ring containing 4 to 12 ring atoms of which at least one ring atom is selected from nitrogen, sulfur, and oxygen, and which may, unless otherwise specified, be
carbon or nitrogen linked, and of which a -CH₂- group can optionally be replaced by a -C(O)-. Ring sulfur atoms may be optionally oxidized to form S-oxides. Ring nitrogen atoms may be optionally oxidized to form N-oxides. Illustrative examples of the term "heterocyclyl" include, but are not limited to, 1,3-benzodioxolyl, 3,5-dioxopiperidinyl, furanyl, imidazolyl, indolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholino, 2-oxa-5-azabicyclo[2.2.1]hept-5-yl, oxazolyl, 2-oxopyrrolidinyl, 2-oxo-1,3-thiazolidinyl, piperazinyl, piperidyl, 2H-pyranyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyridazinyl, 4-pyridonyl, quinolyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolyl, thiadiazolyl, thiazolindinyl, thiomorpholino, thiophenyl, pyridine-N-oxidyl and quinoline-N-oxidyl.

5- or 6-Membered Heterocyclyl - In one aspect, "heterocyclyl" may be "5- or 6-membered heterocyclyl," which refers to a saturated, partially saturated, or unsaturated, monocyclic ring containing 5 or 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur, and oxygen, and of which a -CH₂- group may be optionally replaced by a -C(O)- group. Unless otherwise specified, "5- or 6-membered heterocyclyl" groups may be carbon or nitrogen linked. Ring nitrogen atoms may be optionally oxidized to form an N-oxide. Ring sulfur atoms may be optionally oxidized to form S-oxides. Illustrative examples of "5- or 6-membered heterocyclyl" include, but are not limited to, 3,5-dioxopiperidinyl, furanyl, imidazolyl, isothiazolyl, isoxazolyl, morpholino, oxazolyl, 2-oxopyrrolidinyl, 2-oxo-1,3-thiazolidinyl, piperazinyl, piperidyl, 2H-pyranyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyridazinyl, 4-pyridonyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolyl, thiadiazolyl, thiazolindinyl, thiomorpholino, thiophenyl, pyridine-N-oxidyl.

6-Membered Heterocyclyl - In another aspect, "heterocyclyl" and "5- or 6-membered heterocyclyl" may be "6-membered heterocyclyl," which refers to a saturated, partially saturated, or unsaturated, monocyclic ring containing 6 ring atoms, of which at least one ring atom is selected from nitrogen, sulfur, and oxygen, and of which a -CH₂- group may be optionally replaced by a -C(O)- group. Unless otherwise specified, "6-membered heterocyclyl" groups may be carbon or nitrogen linked. Ring nitrogen atoms may be optionally oxidized to form an N-oxide. Ring sulfur atoms may be optionally oxidized to form S-oxides. Illustrative examples of "6-membered heterocyclyl" include, but are not limited to, 3,5-dioxopiperidinyl, morpholino,
piperazinyl, piperidinyl, 2H-pyranyl, pyrazinyl, pyridazinyl, pyridinyl, and pyrimidinyl.

6-Membered Heteroaryl - In still another aspect, "heterocyclyl", "5- or 6-membered heterocyclyl," and "6-membered heterocyclyl" may be "6-membered heteroaryl." The term "6-membered heteroaryl" is intended to refer to a monocyclic, aromatic heterocyclyl ring containing 6 ring atoms. Ring nitrogen atoms may be optionally oxidized to form an N-oxide. Ring sulfur atoms may be optionally oxidized to form S-oxides. Illustrative examples of the term "6-membered heteroaryl" include, but are not limited to, pyrazinyl, pyridazinyl, pyrimidinyl, and pyridinyl.

Where a particular R group (e.g. R³¹, R³⁰, etc.) is present in a compound of Formula (I) more than once, it is intended that each selection for that R group is independent at each occurrence of any selection at any other occurrence. For example, the -N(R)₂ group is intended to encompass: 1) those -N(R)₂ groups in which both R substituents are the same, such as those in which both R substituents are, for example, Ci₆alkyl; and 2) those -N(R)₂ groups in which each R substituent is different, such as those in which one R substituent is, for example, H, and the other R substituent is, for example, carbocyclyl.

Unless specifically stated, the bonding atom of a group may be any suitable atom of that group; for example, propyl includes prop-1-yl and prop-2-yl.

Effective Amount - As used herein, the phrase "effective amount" means an amount of a compound or composition which is sufficient enough to significantly and positively modify the symptoms and/or conditions to be treated (e.g., provide a positive clinical response). The effective amount of an active ingredient for use in a pharmaceutical composition will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient(s) being employed, the particular pharmaceutically-acceptable excipient(s)/carrier(s) utilized, and like factors within the knowledge and expertise of the attending physician.

In particular, an effective amount of a compound of Formula (I) for use in the treatment of cancer
is an amount sufficient to symptomatically relieve in a warm-blooded animal such as man, the
symptoms of cancer and myeloproliferative diseases, to slow the progression of cancer and
myeloproliferative diseases, or to reduce in patients with symptoms of cancer and
myeloproliferative diseases the risk of getting worse.

Leaving Group - As used herein, the phrase "leaving group" is intended to refer to groups readily
displaceable by a nucleophile such as an amine nucleophile, and alcohol nucleophile, or a thiol
nucleophile. Examples of suitable leaving groups include halo, such as chloro and bromo, and
sulfonyloxy group, such as methanesulfonyloxy and toluene-4-sulfonyloxy.

Optionally substituted - As used herein, the phrase "optionally substituted," indicates that
substitution is optional and therefore it is possible for the designated group to be either
substituted or unsubstituted. In the event a substitution is desired, any number of hydrogens on
the designated group may be replaced with a selection from the indicated substituents, provided
that the normal valency of the atoms on a particular substituent is not exceeded, and that the
substitution results in a stable compound.

In one aspect, when a particular group is designated as being optionally substituted with "one or
more" substituents, the particular may be unsubstituted. In another aspect, the particular group
may bear one substituent. In another aspect, the particular substituent may bear two substituents.
In still another aspect, the particular group may bear three substituents. In yet another aspect, the
particular group may bear four substituents. In a further aspect, the particular group may bear
one or two substituents. In still a further aspect, the particular group may be unsubstituted, or
may bear one or two substituents.

Pharmaceutically Acceptable - As used herein, the term "pharmaceutically acceptable" refers to
those compounds, materials, compositions, and/or dosage forms which are, within the scope of
sound medical judgment, suitable for use in contact with the tissues of human beings and animals
without excessive toxicity, irritation, allergic response, or other problem or complication,
commensurate with a reasonable benefit/risk ratio.
Protecting Group - As used herein, the term "protecting group" is intended to refer to those groups used to prevent selected reactive groups (such as carboxy, amino, hydroxy, and mercapto groups) from undergoing undesired reactions.

Illustrative examples of suitable protecting groups for a hydroxy group include, but are not limited to, an acyl group; alkanoyl groups such as acetyl; aroyl groups, such as benzoyl; silyl groups, such as trimethylsilyl; and arylmethyl groups, such as benzyl. The deprotection conditions for the above hydroxy protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively a silyl group such as trimethylsilyl may be removed, for example, by fluoride or by aqueous acid; or an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon.

Illustrative examples of suitable protecting groups for an amino group include, but are not limited to, acyl groups; alkanoyl groups such as acetyl; alkoxy carbonyl groups, such as methoxycarbonyl, ethoxycarbonyl, and t-butoxycarbonyl; arylmethoxycarbonyl groups, such as benzyloxy carbonyl; and aroyl groups, such benzoyl. The deprotection conditions for the above amino protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxy carbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a t-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric, phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxy carbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid, for example boron trichloride). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group, which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine or 2-hydroxyethylamine, or with hydrazine. Another suitable protecting group for an amine is, for example, a cyclic ether such as tetrahydrofuran, which may
be removed by treatment with a suitable acid such as trifluoroacetic acid.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art, or they may be removed during a later reaction step or work-up.

With reference to substituent R\(^1\) for illustrative purposes, the following substituent definitions have the indicated meanings:

\[
-N(R^{1a})_2 = \begin{array}{c}
\text{R}^{1a} \\
\text{R}^{1a} \\
\end{array},
\]

\[
-N(R^{1a})_{\text{O}}C(\text{O})(R^{1a})_2 = \begin{array}{c}
\text{R}^{1a} \\
\text{R}^{1a} \\
\text{R}^{1a} \\
\end{array},
\]

\[
-N(R^{1a})_{\text{C}(\text{O})(\text{N})(R^{1a})_2} = \begin{array}{c}
\text{R}^{1a} \\
\text{R}^{1a} \\
\text{R}^{1a} \\
\end{array},
\]

\[
-N(R^{1a})_2 \text{C}(\text{O})(\text{S})(\text{O})(\text{R}^{1a})_2 = \begin{array}{c}
\text{R}^{1a} \\
\text{R}^{1a} \\
\text{R}^{1a} \\
\end{array},
\]

\[
-N(R^{1a})_2 \text{N}(\text{R}^{1a})_2 = \begin{array}{c}
\text{R}^{1a} \\
\text{R}^{1a} \\
\text{R}^{1a} \\
\end{array},
\]

\[
-C(\text{O})\text{R}^{1b} = \begin{array}{c}
\text{R}^{1b} \\
\text{R}^{1b} \\
\end{array},
\]

\[
-C(\text{O})_2 \text{R}^{1a} = \begin{array}{c}
\text{R}^{1a} \\
\text{R}^{1a} \\
\end{array}.
\]
The compounds discussed herein in many instances were named and/or checked with ACD/Name by ACD/Labs®.

Compounds of Formula (I) may form stable pharmaceutically acceptable acid or base salts, and in such cases administration of a compound as a salt may be appropriate. Examples of acid addition salts include acetate, adipate, ascorbate, benzoate, benzenesulfonate, bicarbonate, bisulfate, butyrate, camphor, camphorsulfonate, choline, citrate, cyclohexyl sulfamate, diethylenediamine, ethanesulfonate, fumarate, glutamate, glycolate, hemisulfate, 2-hydroxyethyl-
sulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, hydroxymaleate, lactate, malate, maleate, methanesulfonate, meglumine, 2-naphthalenesulfonate, nitrate, oxalate, pamoate, persulfate, phenylacetate, phosphate, diphosphate, picrate, pivalate, propionate, quinate, salicylate, stearate, succinate, sulfamate, sulfanilate, sulfate, tartrate, tosylate (p-toluenesulfonate), trifluoroacetate, and undecanoate. Examples of base salts include ammonium salts; alkali metal salts such as sodium, lithium and potassium salts; alkaline earth metal salts such as aluminum, calcium and magnesium salts; salts with organic bases such as dicyclohexylamine salts and N-methyl-D-glucamine; and salts with amino acids such as arginine, lysine, ornithine, and so forth. Also, basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl halides; dialkyl sulfates such as dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl halides; arylalkyl halides such as benzyl bromide and others. Non-toxic physiologically-acceptable salts are preferred, although other salts may be useful, such as in isolating or purifying the product.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water, which is removed in vacuo or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion-exchange resin.

Some compounds of Formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers. The invention further relates to any and all tautomeric forms of the compounds of Formula (I).

It is also to be understood that certain compounds of Formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms.

Additional embodiments of the invention are as follows. These additional embodiments relate to compounds of Formula (I) and pharmaceutically acceptable salts thereof. Such specific
substituents may be used, where appropriate, with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Ring A

5 In one aspect, Ring A is pyridinyl.

In another aspect, Ring A is pyrimidinyl.

In yet another aspect, Ring A is selected from pyridin-2-yl and pyrimidin-2-yl.

10 \( R^1 \)

In one aspect, \( R^1 \) is halo.

In another aspect, \( R^1 \) is selected from fluoro and chloro.

15 In still another aspect, \( R^1 \) is fluoro.

In yet another aspect, \( R^1 \) is chloro.

20 \( R^2 \)

In one aspect, \( R^2 \) is selected from methyl, C2-6alkyl, and carbocyclyl, wherein said methyl is substituted with at least one \( R^{20} \), and wherein said C2-6alkyl and carbocyclyl are optionally substituted on carbon with one or more \( R^{20} \);

\( R^{20} \) is selected from \(-OR^{20a} \) and \(-C(O)N(R^{20a})_2 \); and

25 \( R^{20a} \) is selected from H and C_{1-6}alkyl.

In another aspect, \( R^2 \) is selected from methyl, ethyl, cyclopropyl, wherein said methyl is substituted on carbon with at least one \( R^{20} \), and wherein said ethyl and cyclopropyl are optionally substituted with one or more \( R^{20} \);

30 \( R^{20} \) is selected from \(-OR^{20a} \) and \(-C(O)N(R^{20a})_2 \); and

\( R^{20a} \) is selected from H and methyl.
In still another aspect, $R^2$ is methyl, wherein said methyl is substituted on carbon with at least one $R^{20}$; $R^{20}$ is selected from $-OR^{20a}$ and $-C(O)N(R^{20a})_2$; and $R^{20a}$ is selected from $H$ and $C_{1-6}$alkyl.

In yet another aspect, $R^2$ is selected from cyclopropyl, ethyl, hydroxyethyl, hydroxymethyl, methoxymethyl, and methylaminocarbonylmethyl.

In a further aspect, $R^2$ is selected from ethyl, hydroxyethyl, hydroxymethyl, methoxymethyl, and methylaminocarbonylmethyl.

In one aspect, $R^3$ is halo.

In another aspect, $R^3$ is fluoro.

$n$

In one aspect, $n$ is 1.

In another aspect, $n$ is 2.

$R^3$ and $n$

In one aspect, $R^3$ is halo; and $n$ is 1.

In another aspect, $R^3$ is halo; and $n$ is 2.

In still another aspect, $R^3$ is fluoro; and $n$ is 1 or 2.
In yet another aspect, $R^3$ is fluoro; and
$n$ is 1.

5 In a further aspect, $R^3$ is fluoro; and
$n$ is 2.

In yet a further aspect, $R^3$ is halo; and
$n$ is 1 or 2.

10 **Ring A, $R^3$, and $n$**

In one aspect, **Ring** A is selected from pyridinyl and pyrimidinyl;
$R^3$ is halo; and
$n$ is 1 or 2.

15 In another aspect, **Ring** A is selected from pyridinyl and pyrimidinyl;
$R^3$ is fluoro; and
$n$ is 1 or 2.

20 In still another aspect, **Ring** A is selected from pyridin-2-yl and pyrimidin-2-yl;
$R^3$ is fluoro; and
$n$ is 1 or 2.

25 In yet another aspect, **Ring** A, $R^3$, and $n$ together form a group selected from 3,5-difluoropyridin-2-yl, 5-fluoropyridin-2-yl, and 5-fluoropyrimidin-2-yl.

**Ring A, $R^1$, $R^2$, $R^3$, and $n$**

In one aspect, **Ring** A is selected from pyridinyl and pyrimidinyl;
$R^1$ is halo.

30 $R^3$ is selected from methyl, C2-6alkyl, and carbocyclyl, wherein said methyl is substituted with at least one $R^{20}$, and wherein said C2-6alkyl and carbocyclyl are optionally substituted on carbon
with one or more $R^{20}$;
$R^{20}$ is selected from $-OR^{20a}$ and $-C(O)N(R^{20a})_2$;
$R^{20a}$ is selected from $H$ and $C_1$-alkyl.
$R^3$ is halo; and

5  \( n \) is 1 or 2.

In another aspect,
Ring A is selected from pyridinyl and pyrimidinyl;
$R^1$ is halo.

10 $R^2$ is methyl, wherein said methyl is substituted one carbon with at least one $R^{20}$;
$R^{20}$ is selected from $-OR^{20a}$ and $-C(O)N(R^{20a})_2$;
$R^{20a}$ is selected from $H$ and $C_1$-alkyl.
$R^3$ is halo; and

n is 1 or 2.

15 In still another aspect,
Ring A is selected from pyridin-2-yl and pyrimidin-2-yl;
$R^1$ is selected from fluoro and chloro;

20 $R^2$ is selected from methyl, ethyl, cyclopropyl, wherein said methyl is substituted on carbon with
at least one $R^{20}$, and wherein said ethyl and cyclopropyl are optionally substituted with one or
more $R^{20}$;
$R^{20}$ is selected from $-OR^{20a}$ and $-C(O)N(R^{20a})_2$;
$R^{20a}$ is selected from $H$ and methyl;
$R^3$ is fluoro; and

25 \( n \) is 1 or 2.

In yet another aspect,
Ring A is selected from pyridin-2-yl and pyrimidin-2-yl;
$R^1$ is selected from fluoro and chloro;

30 $R^2$ is selected from methyl, wherein said methyl is substituted on carbon with at least one $R^{20}$;
$R^{20}$ is selected from $-OR^{20a}$ and $-C(O)N(R^{20a})_2$;
R\textsuperscript{2oa} is selected from H and methyl;
R\textsuperscript{3} is fluoro; and
n is 1 or 2.

In a further aspect, R\textsuperscript{1} is selected from fluoro and chloro;
R\textsuperscript{2} is selected from cyclopropyl, ethyl, hydroxyethyl, hydroxymethyl, methoxymethyl, and N-methylaminocarbonylmethyl; and
Ring A, R\textsuperscript{3}, and n together form a group selected from 3,5-difluoropyridin-2-yl, 5-fluoropyridin-2-yl and 5-fluoropyrimidin-2-yl.

In one aspect, the compound of Formula (I) may be a compound of Formula (Ia):

\begin{center}
\includegraphics[width=0.5\textwidth]{formula.png}
\end{center}

or a pharmaceutically acceptable salt thereof, wherein Ring A, R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, and n are as defined hereinabove.

In another aspect, the compound of Formula (I) may be a compound of Formula (Ib):
or a pharmaceutically acceptable salt thereof, wherein Ring A, R₁, R₂, R₃, and n are as defined hereinabove.

In one aspect, the compound of Formula (I) may be a compound of Formula (Ic):

or a pharmaceutically acceptable salt thereof, wherein R¹, R², and R³ are as defined hereinabove, and wherein E is selected from N, CH, and CR³.

In another aspect, the compound of Formula (I) may be a compound of Formula (Id):

20
or a pharmaceutically acceptable salt thereof, wherein $R^1$, $R^2$, and $R^3$ are as defined hereinabove, and wherein $E$ is selected from N, CH, and CR$^3$.

In one aspect, the present invention provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as illustrated by the Examples, each of which provides a further independent aspect of the invention.

In another aspect, the present invention provides a compound of Formula (I) selected from:

- 5-Chloro-$N^2$-[(15)-1-(5-fluoropyridin-2-yl)propyl]- $N^4$-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;
- (35)-3-[(5-Chloro-4-[(5-methyl-1H-pyrazol-3-yl)amino]pyrimidin-2-yl)amino]-3-(5-fluoropyridin-2-yl)-$N$-methylpropanamide;
- (3i?)-3-[(5-Chloro-4-[(5-methyl-1H-pyrazol-3-yl)amino]pyrimidin-2-yl)amino]-3-(5-fluoropyridin-2-yl)-$N$-methylpropanamide;
- 5-Chloro-$N^2$-[(li?)-1-(5-fluoropyridin-2-yl)-2-methoxyethyl]- $N^4$-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;
- 5-Chloro-$N^2$-[(15)-1-(5-fluoropyridin-2-yl)-2-methoxyethyl]- $N^4$-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;
5-Fluoro-2-[[(R)-1-(5-fluoropyridin-2-yl)-2-methoxyethyl]-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;  
5-Fluoro-N2-[(1S)-1-(5-fluoropyridin-2-yl)-2-methoxyethyl]-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;  
5-Fluoro-N2-[(1S)-1-(5-fluoropyridin-2-yl)-2-methoxyethyl]-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;  
(3S)-3-[(5-Chloro-4-[(5-methyl-1H-pyrazol-3-yl)amino]pyrimidin-2-yl)amino]-3-(5-fluoropyridin-2-yl)propan-1-ol;  
(3R)-3-[(5-Chloro-4-[(5-methyl-1H-pyrazol-3-yl)amino]pyrimidin-2-yl)amino]-3-(5-fluoropyridin-2-yl)propan-1-ol;  
5-Chloro-N2-[(15)-1-(5-fluoropyridin-2-yl)propyl]-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;  
(35)-3-[(5-Chloro-4-[(5-methyl-1H-pyrazol-3-yl)amino]pyrimidin-2-yl)amino]-3-(5-fluoropyridin-2-yl)propan-1-ol;  
5-Chloro-N2-[(1S)-1-(3,5-difluoropyridin-2-yl)-2-methoxyethyl]-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;  
(3S)-2-[(5-Chloro-4-[(5-methyl-1H-pyrazol-3-yl)amino]pyrimidin-2-yl)amino]-2-(5-fluoropyridin-2-yl)ethanol;  
5-Chloro-N2-[(1S)-1-(3,5-difluoropyridin-2-yl)-2-methoxyethyl]-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;  
5-Chloro-N2-[(1S)-1-(5-fluoropyrimidin-2-yl)-2-methoxyethyl]-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;  
and  
S-Chloro-N^1-tCl^-1-CS-fluoropyrimidin^y^-y^-methoxyethyl^- N^-CS-methyl-lH-pyrazol-S-yl)pyrimidine -2,4-diamine,  
or pharmaceutically acceptable salt thereof.

In still a further aspect, the present invention provides a compound of Formula (I) selected from:  
5-Chloro-N2-[(1S)-1-(5-fluoropyridin-2-yl)propyl]-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;  
(35)-3-[(5-Chloro-4-[(5-methyl-1H-pyrazol-3-yl)amino]pyrimidin-2-yl)amino]-3-(5-fluoropyridin-2-yl)-N-methylpropanamide;  
5-Chloro-N2-[(1S)-1-(5-fluoropyridin-2-yl)-2-methoxyethyl]-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine;
5-Fluoro-\(N^2\)-[(\(1\)R)-\(1\)-(5-fluoropyridin-2-yl)-2-methoxyethyl]-\(N^4\)-(5-methyl-1\(H\)-pyrazol-3-yl)pyrimidine-2,4-diamine;
5-Fluoro-\(N^2\)-[(\(1\)S)-\(1\)-(5-fluoropyridin-2-yl)propyl]-\(N^4\)-(5-methyl-1\(H\)-pyrazol-3-yl)pyrimidine-2,4-diamine;
(35)-3-({5-Chloro-4-[(5-methyl-1\(H\)-pyrazol-3-yl)amino]pyrimidin-2-yl}amino)-3-(5-fluoropyridin-2-yl)propan-1-ol;
5-Chloro-\(N^2\)-[(5)-cyclopropyl(5-fluoropyridin-2-yl)methyl]-\(N^4\)-(5-methyl-1\(H\)-pyrazol-3-yl)pyrimidine-2,4-diamine;
(2\(S\))-2-((5-Chloro-4-[(5-methyl-1\(H\)-pyrazol-3-yl)amino]pyrimidin-2-yl)amino)-2-(5-fluoropyridin-2-yl)ethanol;
5-Chloro-\(N^2\)-[(\(1\)R)-\(1\)-(3,5-difluoropyridin-2-yl)-2-methoxyethyl]-\(N^4\)-(5-methyl-1\(H\)-pyrazol-3-yl)pyrimidine-2,4-diamine; and
5-Chloro-\(N^2\)-[(\(1\)R)-\(1\)-(5-fluoropyrimidin-2-yl)-2-methoxyethyl]-\(N^4\)-(5-methyl-1\(H\)-pyrazol-3-yl)pyrimidine-2,4-diamine,
or pharmaceutically acceptable salt thereof.

Utility
Typical compounds of Formula (I) are believed to have utility for the treatment of myeloproliferative disorders, myelodysplastic syndrome and cancer by inhibiting the JAK tyrosine kinases, particularly the JAK2 family. Methods of treatment target tyrosine kinase activity, particularly the JAK family activity and more particularly JAK2 activity, which is involved in a variety of myeloproliferative disorders, myelodysplastic syndrome and cancer related processes. Thus, inhibitors of tyrosine kinase, particularly the JAK family and more particularly JAK2, are expected to be active against myeloproliferative disorders such as chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myeloid metaplasia with myelofibrosis, idiopathic myelofibrosis, chronic myelomonocytic leukemia and hypereosinophilic syndrome, myelodysplastic syndromes and neoplastic disease such as carcinoma of the breast, ovary, lung, colon, prostate or other tissues, as well as leukemias, myelomas and lymphomas, tumors of the central and peripheral nervous system, and other tumor types such as melanoma, fibrosarcoma and osteosarcoma. Tyrosine kinase inhibitors, particularly the JAK family inhibitors and more particularly JAK2 inhibitors are also expected to be useful.
for the treatment other proliferative diseases including but not limited to autoimmune, inflammatory, neurological, and cardiovascular diseases.

The compounds of Formula (I) have been shown to inhibit tyrosine kinases, particularly the JAK family and more particularly JAK2, as determined by the JAK2 Assay described herein.

The compounds of Formula (I) should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit tyrosine kinases, particularly the JAK family and more particularly JAK2. These would be provided in commercial kits comprising a compound of this invention.

JAK2 kinase activity may be determined by measuring the kinase's ability to phosphorylate synthetic tyrosine residues within a generic polypeptide substrate using an Amplified Luminescent Proximity Assay (Alphascreen) technology (PerkinElmer, 549 Albany Street, Boston, MA).

To measure JAK2 kinase activity, a commercially available purified enzyme may be used. The enzyme may be C-terminal His6-tagged, recombinant, human JAK2, amino acids 808-end, (Genbank Accession number NM 004972) expressed by baculovirus in Sf21 cells (Upstate Biotechnology MA). After incubation of the kinase with a biotinylated substrate and adenosine triphosphate (ATP) for 60 minutes at room temperature, the kinase reaction may be stopped by the addition of 30 mM ethylenediaminetetraacetic acid (EDTA). The reaction may be performed in 384 well microtitre plates and the reaction products may be detected with the addition of streptavidin coated Donor Beads and phosphotyrosine-specific antibodies coated Acceptor Beads using the EnVision Multilabel Plate Reader after an overnight incubation at room temperature. "Tween 20" is a registered trademark of ICI Americas, Inc.

<table>
<thead>
<tr>
<th>Peptide substrate</th>
<th>TYK2 (Tyr 1054/1055 biotinylated peptide) Cell Signalling Technology #2200B. 402μM stock.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP Km</td>
<td>15 μM</td>
</tr>
</tbody>
</table>
The compounds and salts of the example numbers listed below in Table 1 were tested in the in-vitro assay described above at a concentration of 30 μM, providing the indicated JAK inhibitory %. In most instances, each compound or salt was tested four or more times, and the % inhibition shown below is the average % inhibition. The term "inhibition" refers to the percentage decrease in kinase activity (compared to an untreated sample) by the compound of the indicated example number.

The compounds and salts of the example numbers listed below in Table 1 were tested in the in-vitro assay described above at a concentration of 30 μM, providing the indicated JAK inhibitory %.

### Table 1

<table>
<thead>
<tr>
<th>Example</th>
<th>Inhibition (%) at 30 μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>2(a)</td>
<td>100</td>
</tr>
<tr>
<td>2(b)</td>
<td>99</td>
</tr>
<tr>
<td>3(a)</td>
<td>99</td>
</tr>
<tr>
<td>3(b)</td>
<td>—</td>
</tr>
<tr>
<td>4(a)</td>
<td>100</td>
</tr>
<tr>
<td>4(b)</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>6(a)</td>
<td>100</td>
</tr>
</tbody>
</table>
Thus, in one aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament.

In another aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of myeloproliferative disorders, myelodysplastic syndrome, and cancer, in a warm-blooded animal such as man.

In still another aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of myeloproliferative disorders, myelodysplastic syndrome and cancers (solid and hematologic tumors), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acromegaly, acute and chronic inflammation, bone diseases, and ocular diseases with retinal vessel proliferation, in a warm-blooded animal such as man.

In yet another aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myeloid metaplasia with myelofibrosis, idiopathic myelofibrosis, chronic myelomonocytic leukemia and hypereosinophilic syndrome, myelodysplastic syndromes and cancers selected from oesophageal
cancer, myeloma, hepatocellular, pancreatic, cervical cancer, Ewings sarcoma, neuroblastoma, Kaposi's sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, mesothelioma, renal cancer, lymphoma and leukaemia, in a warm-blooded animal such as man.

In a further aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the production of an anti-proliferative effect, in a warm-blooded animal such as man.

In still a further aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the production of a JAK inhibitory effect.

In yet a further aspect, there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

In one aspect, there is provided a method for treating myeloproliferative disorders, myelodysplastic syndrome, and cancer, in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a method for treating myeloproliferative disorders, myelodysplastic syndrome, and cancers (solid and hematologic tumors), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acromegaly, acute and chronic inflammation, bone diseases, and ocular diseases with retinal vessel proliferation, in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.
In still another aspect, there is provided a method for treating chronic myeloid leukemia, polycythemias, essential thrombocytopenia, myeloid metaplasia with myelofibrosis, idiopathic myelofibrosis, chronic myelomonocytic leukemia and hypereosinophilic syndrome, myelodysplastic syndromes and cancers selected from oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, Ewing's sarcoma, neuroblastoma, Kaposi's sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, mesothelioma, renal cancer, lymphoma and leukaemia, in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In yet another aspect, there is provided a method for producing an anti-proliferative effect in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In a further aspect, there is provided a method for producing a JAK inhibitory effect in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In still a further aspect, there is provided a method for treating cancer in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In yet a further aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating myeloproliferative disorders, myelodysplastic syndrome, and cancer, in a warm-blooded animal such as man.

In one aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating myeloproliferative disorders, myelodysplastic syndrome, and cancers (solid and hematologic tumors), fibroproliferative and differentiative disorders, psoriasis,
rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acromegaly, acute and chronic inflammation, bone diseases, and ocular diseases with retinal vessel proliferation, in a warm-blooded animal such as man.

In another aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treating chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myeloid metaplasia with myelofibrosis, idiopathic myelofibrosis, chronic myelomonocytic leukemia and hypereosinophilic syndrome, myelodysplastic syndromes and cancers selected from oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, Ewings sarcoma, neuroblastoma, Kaposi's sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, mesothelioma, renal cancer, lymphoma and leukaemia, in a warm-blooded animal such as man.

In still another aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the production of an anti-proliferative effect, in a warm-blooded animal such as man.

In yet another further aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the production of a JAK inhibitory effect in a warm-blooded animal such as man.

In a further aspect, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a warm-blooded animal such as man.

In still a further aspect, where reference is made to the treatment (or prophylaxis) of cancer, it may particularly refer to the treatment (or prophylaxis) of mesoblastic nephroma, mesothelioma, acute myeloblastic leukemia, acute lymphocytic leukemia, multiple myeloma, oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, Ewings sarcoma, neuroblastoma, Kaposi's sarcoma, ovarian cancer, breast cancer including secretory breast cancer, colorectal cancer,
cancer, prostate cancer including hormone refractory prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, renal cancer, lymphoma, thyroid cancer including papillary thyroid cancer, mesothelioma, leukaemia, tumors of the central and peripheral nervous system, melanoma, fibrosarcoma including congenital fibrosarcoma and osteosarcoma. More particularly it refers to prostate cancer. In addition, more particularly it refers to SCLC, NSCLC, colorectal cancer, ovarian cancer and/or breast cancer. In a further aspect it may refer to hormone refractory prostate cancer.

In yet a further aspect, there is provided a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

In one aspect, there is provided a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.
Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate; granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl /?-hydroxybenzoate; and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form or in the form of nano or micronized particles together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives such as ethyl or propyl /?-hydroxybenzoate; anti-oxidants such as ascorbic acid); coloring agents; flavoring agents; and/or sweetening agents such as sucrose, saccharine or aspartame.
Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as arachis oil, olive oil, sesame oil or coconut oil or in a mineral oil such as liquid paraffin. The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavoring and/or coloring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a
non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurized aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 4 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. Accordingly, the optimum dosage may be determined by the practitioner who is treating any particular patient.

The anti-cancer treatment defined herein may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of
anti-tumor agents:

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimitabolites (for example antifolates such as fluoropyrimidines including 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea); antitumor antibiotics (for example anthracyclines such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids such as vincristine, vinblastine, vindesine and vinorelbine and taxoids such as taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins such as etoposide and teniposide, amsacrine, topotecan and camptothecin); and proteosome inhibitors (for example bortezomib [Velcade®]); and the agent anegrilide [Agrylin®]; and the agent alpha-interferon;

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxfene and idoxyfentanyl), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors such as marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erb2 antibody trastuzumab [Herceptin™] and the anti-erbbl antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZDl 839), N-(3-ethynlyphenyl)-6,7-bis...
(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morphinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family, for example inhibitors of phosphotidylinositol 3-kinase (PI3K) and for example inhibitors of mitogen activated protein kinase (MEK1/2) and for example inhibitors of protein kinase B (PKB/Akt), for example inhibitors of Src tyrosine kinase family and/or Abelson (AbI) tyrosine kinase family such as AZD0530 and dasatinib (BMS-354825) and imatinib mesylate (GleevecTM); and any agents that modify STAT signalling;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αβ3 function and angiotatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy;

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumor cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumor cell lines and approaches using anti-idiotypic antibodies and approaches using the
immunomodulatory drugs thalidomide and lenalidomide (Revlimg®); and other treatment regimes including: dexamethasone, proteasome inhibitors (including bortezomib), isotretinoin (13-cis retinoic acid), thalidomide, revemid, Rituxamab, ALIMTA, Cephalon's kinase inhibitors CEP-701 and CEP-2563, anti-Trk or anti-NGF monoclonal antibodies, targeted radiation therapy with 131I-metaiodobenzylguanidine (131I-MIBG), anti-G(D2) monoclonal antibody therapy with or without granulocyte-macrophage colony-stimulating factor (GM-CSF) following chemotherapy.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention, or pharmaceutically acceptable salts thereof, within the dosage range described hereinbefore and the other! pharmaceutically-active agent within its approved dosage range.

In addition to its use in therapeutic medicine, compounds of Formula (I) and pharmaceutically acceptable salts thereof are also useful as pharmacological tools in the development and standardization of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of JAK2 in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In any of the above-mentioned pharmaceutical composition, process, method, use, medicament, and manufacturing features of the instant invention, any of the alternate embodiments of the compounds of the invention described herein also apply.

In one aspect, the inhibition of JAK activity particularly refers to the inhibition of JAK2 activity.

Process.
If not commercially available, the necessary starting materials for the procedures such as those described herein may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the described procedure or the procedures
described in the Examples.

It is noted that many of the starting materials for synthetic methods as described herein are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature. The reader is further referred to Advanced Organic Chemistry, 5th Edition, by Jerry March and Michael Smith, published by John Wiley & Sons 2001, for general guidance on reaction conditions and reagents.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in compounds. The instances where protection is necessary or desirable are known to those skilled in the art, as are suitable methods for such protection. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, published by John Wiley and Sons, 1991) and as described hereinabove.

Compounds of Formula (I) may be prepared in a variety of ways. The Processes and Schemes shown below illustrate some methods for synthesizing compounds of Formula (I) and pharmaceutically acceptable salts thereof, and intermediates which may be used for the synthesis of compounds of Formula (I) (wherein \textbf{Ring A}, \textbf{R}^1, \textbf{R}^2, \textbf{R}^3, and \textbf{n}, unless otherwise defined, are as defined hereinabove). Where a particular solvent or reagent is shown in a Scheme or referred to in the accompanying text, it is to be understood that the chemist of ordinary skill in the art will be able to modify that solvent or reagent as necessary. The Processes are not intended to present an exhaustive list of methods for preparing the compounds of Formula (I); rather, additional techniques of which the skilled chemist is aware may be also be used for the compounds' synthesis. The claims are not intended to be limited to the structures shown in the Processes.

The skilled chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples and Scheme herein, to obtain necessary starting materials and products.
1) **Process A** - reacting a compound of Formula (A):

![Formula (A)](image1)

with a compound of Formula (B):

![Formula (B)](image2)

and thereafter if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a pharmaceutically acceptable salt,

wherein L is a leaving group as described hereinabove.

3) **Process B** - reacting a compound of Formula (C):

![Formula (C)](image3)
with a compound of Formula (D):

\[
\begin{align*}
H_2N & \quad \text{R}^2 \\
\text{A} \quad \text{(R}\text{)}^3_n \\
\end{align*}
\]

Formula (D);

and thereafter if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a pharmaceutically acceptable salt,

wherein \( L \) is a leaving group as described hereinabove.

For each of Processes A and B, it is to be understood that protecting groups may be used as necessary. Leaving groups suitable for use in Processes B and C include halo groups such as chloro. The Processes are discussed in more detail below.

Process A - Compounds of Formula (A) and compounds of Formula (B) may be reacted together in the presence of a suitable solvent, examples of which include ketones such as acetone, alcohols such as ethanol and butanol, and aromatic hydrocarbons such as toluene and N-methyl pyrrolid-2-one. Though the reaction should proceed if excess amounts of the compound of Formula (B) are used, the reaction may advantageously occur in the presence of a suitable base, examples of which include inorganic bases such as potassium carbonate and cesium carbonate, and organic bases such as potassium tert-butoxide and sodium tert-butoxide. The reaction may be advantageously performed at a temperature in a range from 0\(^\circ\)C to reflux. Heating the reaction may be particularly advantageous.

In another aspect, compounds of Formula (A) and compounds of Formula (B) may be reacted together under standard Buchwald conditions (for example see \textit{J. Am. Chem. Soc.}, 118, 7215; \textit{J. Am. Chem. Soc.}, 119, 8451; \textit{J. Org. Chem.}, 62, 1568 and 6066), with a suitable base. Examples of suitable bases include inorganic bases such as cesium carbonate, and organic bases such as potassium tert-butoxide. Such a reaction may advantageously occur in the presence of a palladium
catalyst such as palladium acetate. Examples of solvents suitable for such a reaction include toluene, benzene, dioxane, and xylene. The -NH- moiety of the compound of Formula (B) may advantageously be protected with a suitable protecting group, examples of which include protecting groups such as tert-butoxycarbonyl.

Process B - Compounds of Formula (C) and compounds of Formula (D) may be reacted together under conditions similar to those described for the reaction of compounds of Formula (A) with compounds of Formula (B).

Examples

The invention will now be further described with reference to the following illustrative examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations are carried out at room temperature or ambient temperature, that is, in a range of 18-25 °C;

(ii) organic solutions were dried over anhydrous magnesium sulfate unless otherwise stated; evaporation of organic solvent was generally carried out using a rotary evaporator under reduced pressure (4.5 - 30 mmHg) with a bath temperature of up to 60 °C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC or liquid chromatography/mass spectroscopy (LC/MS) and reaction times are given for illustration only;

(v) final products have satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectra data;

(vi) in some instances, compounds of the examples may have been named "enantiomer A" or "enantiomer B." It should be understood that neither designation is intended to imply a particular stereochemical configuration. Rather, naming two compounds of a particular example this way denotes that the first such compound is the enantiomer of the second, and vice-versa.
(vii) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(viii) when given, NMR data is in the form of delta values for major diagnostic protons, given in part per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz in DMSO-d₆ unless otherwise stated;

(ix) chemical symbols have their usual meanings;

(x) solvent ratio was given in volume : volume (v/v) terms;

(xi) intermediates are not necessarily fully purified but their structures and purity are assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(xii) "ISCO" refers to normal phase flash column chromatography using pre-packed silica gel cartridges (12 g, 40 g etc.) used according to the manufacturers instruction obtained from ISCO, Inc, 4700 Superior Street Lincoln, NE, USA;

(xiii) "Biotage" refers to normal phase flash column chromatography using pre-packed silica gel cartridges (12g, 40g, 80g etc.) used according to the manufacturers instruction obtained from Biotage Inc, 1725 Discovery Drive Charlottesville, Virginia 22911, USA;

(xiv) "Gilson" refers to a YMC-AQCl 8 reverse phase HPLC Column with dimension 20 mm/100 and 50 mm/250 in H₂OMeCN with 0.1% TFA as mobile phase unless otherwise stated and used according to the manufacturers instruction obtained from Gilson, Inc. 3000 Parmenter Street, Middleton, WI 53562-0027, U.S.A.;

(xv) "SFC (super critical fluid chromatography)" refers to Analytical SFC (ASC-1000 Analytical SFC System with Diode Array Detector) and/or Preparative SFC (APS-1000 AutoPrep Preparative SFC), used according to the manufacturers instruction obtained from SFC Mettler Toledo AutoChem, Inc. 7075 Samuel Morse Drive Columbia MD 21046, U.S.A.;

(xvi) Parr Hydrogenator or Parr shaker type hydrogenators are systems for treating chemicals with hydrogen in the presence of a catalyst at pressures up to 5 atmospheres (60 psi) and temperatures to 80 °C; and

(xvii) the following abbreviations have been used:

BINAP — 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Following a similar procedure to that of Intermediate 24, the title compound was synthesized from 5-fluoropyridine-2-carbaldehyde and (5)-2-methylpropane-2-sulfinamide. The product was used in subsequent steps without any further purification.

\(^1\)H NMR (CDCl\(_3\)) \(\delta 8.67 (s, 1 \text{ H}) 8.58 (s, 1 \text{ H}) 8.06 (dd, 1 \text{ H}) 7.51 (t, 1 \text{ H}) 1.20 (s, 9 \text{ H}).\)
**Intermediate 2**

(S,S)-N-[(15')-l-(5-Fluoropyridin-2-yl)propyll]-2-methylpropane-2-sulfinamide

To a solution of (S)-N-[(5-fluoropyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide (Intermediate 1, 1.5 g, 6.58 mmol) in CH₂Cl₂ (10 ml) at -45 °C was added ethylmagnesium bromide (1.0 M in MTBE, 6.6 ml, 6.6 mmol) drop-wise. The reaction mixture was stirred at -4 °C for 30 minutes and to it was added water. The layers were separated and to the organic layer was concentrated. Column chromatography on silica gel (Biotage, 30-50% EtOAc/CH₂Cl₂) gave the title compound (higher i?/on TLC) as a solid (485 mg, 29%).

1H NMR (CDCl₃) δ 8.39 (d, 1 H) 7.29 - 7.41 (m, 1 H) 7.21 - 7.24 (m, 1 H) 4.60 (d, 1 H) 4.31 (q, 2 H) 1.22 - 1.27 (s, 9 H) 0.86 (t, 3 H).

Note: Ss denotes that the configuration of sulfur is S.

**Intermediate 3**

[(15Vl-(5-Fluoropyridin-2-yl)propyl]amine, hydrochloride salt

Following a similar procedure to the one used for the synthesis of Intermediate 2, the title salt was synthesized from (S)-N-[(15')-l-(5-fluoropyridin-2-yl)propyll]-2-methylpropane-2-sulfinamide (Intermediate 2).

1H NMR δ 8.64 (s, 1 H) 8.59 (s, 2 H) 7.77 - 7.92 (m, 1 H) 7.64 (dd, 1 H) 4.33 (d, 1 H) 1.72 - 1.97 (m, 2 H) 0.75 (t, 3 H).

**Intermediate 4**

2,5-Dichloro- N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine

To a solution of 5-methyl-1H-pyrazol-3-amine (2.78 g, 27.3 mmol) in absolute EtOH (30 ml) was added triethylamine (5 ml) and 2,4,5-trichloropyrimidine (5.0 g, 27.3 mmol) and the resulting solution was aged at room temperature for 12 hours. The mixture was partitioned between EtOAc and H₂O, the organic layer was washed with brine and dried. The solvents were removed under reduced pressure to give the title compound (4.1 g). LC-MS: 245 [M+H].

**Intermediate 5**

N-[(1E)-(5-Fluoropyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide
5-Fluoro-2-fermylpyridine (5 g, 40 mmol), racemic \( t \)-butyl sulfinamide (9.7 g, 80 mmol) were dissolved in DCM (100 mL) and CuSO\(_4\) (12.8 g, 80 mmol) was added. The reaction mixture was stirred overnight at rt under nitrogen atmosphere. After completion of the reaction as indicated by TLC, the reaction mixture was filtered through Celite® and washed with DCM. The filtrate was evaporated in vacuo to obtain a light yellow oil, which was purified by column chromatography (Hexane/EtOAc = 80:20) to provide the title compound (7.2 g, 82%) as a white solid.

**Intermediate 6**

**Ethyl 3-[(\( t \)-butylsulfinyl)amino]-3-(5-fluoropyridin-2-yl)propanoate**

To a stirred solution of LDA (26.7 mL of 2M solution, 53.4 mmol) in anhydrous TBME (150 mL) was added drop-wise a solution of EtOAc (4.47 g, 50.9 mmol) in TBME (20 mL) at -78°C under nitrogen atmosphere. After stirring for 30 min, to this was added drop-wise a solution of N-[(\( t \)-ethyl)-(5-fluoropyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide (Intermediate 5, 5.8 g, 25.43 mmol) in TBME (30 mL). After stirring for 2 hours at -78°C (completion of the reaction as indicated by TLC), the reaction mixture was quenched by saturated ammonium chloride and warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layer was dried (Na\(_2\)SO\(_4\)), and evaporated to provide the title compound (5.2 g, 68%) as a mixture of diastereomers (higher RF is major, lower RF is minor), after purification by column chromatography (Hexane: EtOAc = 50:50).

LC-MS: 317 [M+H]

**Intermediate 7**

**3-[(\( t \)-Butylsulfinyl)amino]-3-(5-fluoropyridin-2-yl)propanoic acid**

To a stirred solution of ethyl 3-[(\( t \)-butylsulfinyl)amino]-3-(5-fluoropyridin-2-yl)propanoate (Intermediate 6, 1.2 g, 3.8 mmol) in MeOH (8 mL) and THF (8 mL) was added a solution of LiOH (480 mg, 20 mmol) in H\(_2\)O (4 mL). After stirring for 2 hours at room temperature (at which point the reaction was determined by TLC to be complete), the reaction mixture was acidified with 1M citric acid and extracted with EtOAc (3X). The combined organic layers were dried (Na\(_2\)SO\(_4\)), and evaporated to obtain the title compound (910 mg, 84%) as a thick oil.

LC-MS: 289 [M+H]
**Intermediate 8**

3-[(fer?-Butylsulfinyl)amino]-3-(5-fluoropyridin-2-yl)- N-methylpropanamide

To a stirred solution of 3-[(fer-butylsulfinyl)amino]-3-(5-fluoropyridin-2-yl)propanoic acid (Intermediate 7, 900mg, 3.12mmol), MeNH₂-HCl (63.1 mg, 0.936 mmol) and HATU (2.37g, 6.24 mmol) in anhydrous DMF (3OmL) was added DIPEA (5.13 mL, 30 mmol). The reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. After the reaction was determined by TLC to be complete, the reaction mixture was diluted with EtOAc, and washed with H₂O, saturated NaHCO₃(aq) and brine. The organic layer was dried over Na₂SO₄, and evaporated to obtain a residue (320mg). Purification by column chromatography (DCM / MeOH = 90:10) afforded the title compound (280mg, 29%) as a white solid.

LC-MS: 302 [M+H]

**Intermediate 9**

3-Amino-3-(5-fluoropyridin-2-yl)- N-methylpropanamide. hydrochloride salt

To a stirred solution of 3-[(fer-butylsulfinyl)amino]-3-(5-fluoropyridin-2-yl)- N-methylpropanamide (Intermediate 8, 280 mg, 0.73 mmol) in EtOAc (10mL) was added 4M HCl (2 mL in dioxane) under nitrogen atmosphere. The reaction mixture was stirred for 2 hours at room temperature, during which time a precipitate formed. The reaction mixture was diluted with TBME (10 mL) and the precipitate was filtered, washed with TBME (10 mL) and dried overnight, providing the title salt (175 mg, 95%) as a tan solid. LC-MS: 198 [M+H]. ¹H NMR (500 MHz) δ: 2.48 (s, 3H), 2.85-2.77 (m, 2H), 4.71-4.70 (m, 1H), 7.58 (dd, IH), 7.76 (ddd, IH), 8.14 (d, IH), 8.59 (s, IH).

**Intermediate 10**

N-(2-(fer?-Butyldimethylsilyloxy)ethyldiene)-2-methylpropane-2-sulfinamide

To a suspension of rac-2-methylpropane-2-sulfinamide (3.10 g, 26 mmol) and CuSΘ₄ (8.3 g, 52 mmol) in 60 mL DCM, was added têt-butyldimethylsilyloxy acetaldehyde (5.0 g, 26 mmol) at room temperature. The mixture was stirred at room temperature for 18 hours and then filtered through a Celite® pad followed by washing with DCM. The filtrate was concentrated in vacuo and then purified by column chromatography (20 to 40% EtOAc/α-haxane) to give the title...
compound (6.59 g, 92%) as a pale yellow oil.

**Intermediate 11**

\( N-(2-(\text{fer?-Butyldimethylsilyloxy})\text{Vl-(5-fluoropyridin-2-yl})\text{ethylV2-methylpropane-2-sulf}} \text{namide} \)

To a solution of 2-bromo-5-fluoropyridine (5.2 g, 29 mmol) in 80 mL of anhydrous MTBE was slowly added a 1.7M solution of LDA in pentane (21 mL, 36 mmol) at -78°C. After being stirred for 30 minutes at -78°C, a solution of \( N-(2-(\text{tert-butyldimethylsilyloxy})\text{ethylidene})-2\)-methylpropane-2-sulfinamide (Intermediate 10, 6.59 g, 24 mmol) in 15 mL of anhydrous MTBE was slowly added into the reaction mixture and stirred for an additional 2 hours at the same temperature. The reaction mixture was quenched with saturated NH4Cl (aq) solution, extracted with EtOAc, and dried over anhydrous Na2SO4. The combined organic layers were concentrated \textit{in vacuo} and then purified by column chromatography (30% EtOAc/hexanes) to give the title compound (8.0 g, 90%) as a viscous oil.

LC-MS: 375 [M+H]

**Intermediate 12**

\( \text{tert-hvXyX} \text{[1-(5-fluoropyridin-2-yl)-2-hydroxyethyl]carbamate} \)

To a solution of \( N-(2-(\text{tert-butyldimethylsilyloxy})\text{l-(5-fluoropyridin-2-yl})\text{ethyl})-2\)-methylpropane-2-sulfinamide (Intermediate 11, 1.59 g, 6 mmol) in 50 mL of EtOAc, was slowly added a 4M solution of HCl in dioxane (4.6 mL) at room temperature. The reaction mixture turned cloudy, which was followed by the precipitation of a white solid. After stirring for 2 hours at room temperature, diethyl ether (50mL) was added to complete precipitation of a desired product. After standing for 30 minutes at room temperature, the resulting liquid portion was removed by decantation. The remaining solid portion was dried under vacuum, and used without further purification for the next step. The solid was added into a solution of 20mL of water, 40mL of THF and 4.8mL of 5N-NaOH followed by BoC2O (1.7g) at room temperature. After being stirred at room temperature for 2 hours, the reaction mixture was extracted with EtOAc, and dried over anhydrous Na2SO4. The combined organic layers were concentrated \textit{in vacuo} and then purified by column chromatography (40% EtOAc/hexanes) to give the title compound (1.29g, 84%) as a pale yellow oil.

LC-MS: 257 [M+H]
Intermediate 13

1-(5-Fluoropyridin-2-yl)-2-methoxyethanamine, hydrochloride salt

To a solution of a tert-butyl [l-(5-fluoropyridin-2-yl)-2-hydroxyethyl]carbamate (Intermediate 12, 1.27 g, 5 mmol) in 18 mL of anhydrous THF, was slowly added 20% potassium-t-butoxide solution in THF at -15°C. After stirring for 20 minutes at the same temperature, 0.32 mL of MeI was added, and the mixture was then allowed to warm up to room temperature. The reaction mixture was quenched with saturated ammonium chloride solution, extracted with EtOAc, and dried over anhydrous Na₂SO₄. The combined organic layers were concentrated in vacuo and then purified by column chromatography (20-30% EtOAc/hexanes) to give tert-butyl [l-(5-fluoropyridin-2-yl)-2-methoxyethyl]carbamate (0.58 g, 45%) as a viscous oil. This oil was then dissolved in EtOAc (10 mL) and treated with 4M HCl in dioxane. After stirring 2 hours at room temperature, diethyl ether (20 mL) was added to complete the precipitation of the desired product. After standing for 30 minutes at room temperature, the resulting liquid portion was removed by decantation. The remaining solid portion was dried under vacuum, providing the highly moisture sensitive title salt (267 mg, 72%) as a colorless solid.

LC-MS: 171 [M+H]. ¹H NMR (500 MHz) δ 3.23 (s, 3H), 3.69 (d, 2H), 4.55 (m, 1H), 7.67 (m, 1H), 7.82 (m, 1H) 8.59 (d, 1H) 8.65 (br, 2H).

Intermediate 14

2-Chloro-5-fluoro-N-(5-methyl-l H-pyrazol-3-yl)pyrimidin-4-amine

To a solution of 5-methyl-l H-pyrazol-3-amine (612 mg, 6.0 mmol) in absolute EtOH (10 ml) was added triethylamine (1.1 ml) and 2,4-dichloro-5-fluoropyrimidine (1.0 g, 6.0 mmol). The resulting solution was stirred at room temperature for 12 hours. The mixture was partitioned between EtOAc and water. The organic layer was washed with brine and dried. The solvent was removed under reduced pressure to give the title compound as a solid (679 mg).

LC-MS: 228 [M+H].

Intermediate 15

N-[l-(5-Fluoropyridin-2-yl)-3-hydroxypropyl]-2-methylpropane-2-sulfinamide

Ethyl 3-[t(ert-butylsulfanyl)amino]-3-(5-fluoropyridin-2-yl)propanoate (Intermediate 6, 1.6 g,
5.06 mmol) was dissolved in THF (40 mL) and cooled to 0°C. To this solution was added LiBELi (318 mg, 15 mmol) in small portions under a nitrogen atmosphere. After stirring at room temperature overnight (after which the reaction was determined by TLC to be complete), the reaction mixture was quenched with methanol at 0°C and treated with saturated NH4Cl (aq) solution (5 mL). The organic solvent was removed in vacuo and extracted with EtOAc (2x). The combined organic layers were dried (Na2SCM) and purified by column chromatography (EtOAc/MeOH = 98:2) to give the title compound (920 mg, 66%).

LC-MS: 275 [M+H].

Intermediate 16
3-Amino-3-(5-fluoropyridin-2-yl)propan-1-ol hydrochloride salt
N-[1-(5-Fluoropyridin-2-yl)-3-hydroxypropyl]-2-methylpropane-2-sulfinamide (Intermediate 15, 920 mg, 3.35 mmol) was dissolved in EtOAc (20 mL). To this solution was added 4N HCl (5 mL/dioxane) under a nitrogen atmosphere. The reaction mixture was stirred for 2 hours at room temperature, giving a precipitate. The reaction mixture was diluted with TBME (20 mL) and the precipitate was filtered, washed with TBME (10 mL), and dried to provide the title salt (560 mg, 81%) as a white solid.

LC-MS: 171 [M+H]. 1H NMR (500 MHz) δ 1.88-1.94 (m, 1H), 2.01-2.05 (m, 1H), 3.23-3.25 (m, 1H), 3.36-3.39 (m, 1H), 4.46 (m, 1H), 7.63 (dd, IH), 7.80 (ddd, IH), 8.59 (d, IH), 8.60 (br, 2H).

Intermediate 17
Ethyl 3,5-difluoropyridine-2-carboxylate
3,5-Difluoropyridine-2-carbonitrile (3.5 g, 25 mmol) was dissolved in EtOH (50 mL) and 4N HCl/1,4-dioxane (50 mL) was added. This reaction mixture was refluxed for 24 hours under a nitrogen atmosphere. The reaction mixture was concentrated, extracted with ethyl acetate (100 mL), and washed with saturated NaHCO3. The organic layer was dried over Na2SO4, and concentrated under reduced pressure. Purification by column chromatography (EtOAc : Hexanes = 1:9) gave the title compound (3.1 g, 69%) as a semi solid.

LC-MS: 188 [M+H].
**Intermediate 18**

3,5-Difluoropyridin-2-yl)methanol

A stirred solution of ethyl 3,5-difluoropyridine-2-carboxylate (Intermediate 17, 3.1 g, 16.57 mmol) in anhydrous THF (100 mL) was cooled to 0°C. To this solution was added portion-wise LiBH₄ (1.1g, 50 mmol) under a nitrogen atmosphere. After 30 minutes of stirring at 0°C, the reaction mixture was warmed to room temperature and stirred overnight. After cooling to 0°C, the reaction mixture was quenched with MeOH, followed by saturated NH₄Cl (aq) solution. After most of the organic solvent was removed by evaporation, the residue was diluted with H₂O and extracted with EtOAc (2x). The combined organic layers were dried over Na₂SO₄, and evaporated to give the title compound (1.7g, 71%).

LC-MS: 146 [M+H]

**Intermediate 19**

3,5-Difluoropyridine-2-carbaldehyde

To a stirred solution of 3,5-difluoropyridin-2-yl)methanol (Intermediate 18, 1.7 g, 11.72 mmol) in DCM (100 mL) was added Dess-Martin periodinane (DMP) (8.45 g, 19.92 mmol). The resulting solution was stirred at room temperature overnight under a nitrogen atmosphere. The reaction mixture was diluted with DCM and washed with saturated NaHCO₃ (2x), H₂O, and brine. The combined organic layers were dried over Na₂SO₄, and concentrated. Purification by column chromatography (EtOAc:Hexane = 2:8) provided the title compound (1.4g, 80%) as a thick oil.

LC-MS: 144 [M+H]

**Intermediate 20**

N-[(E)-(3,5-Difluoropyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide

The title compound was prepared using a procedure similar to the one described for the synthesis of Intermediate 6 using 3,5-difluoropyridine-2-carbaldehyde (Intermediate 19) as the starting material. LC-MS: 247 [M+H].

**Intermediate 21**

N-[l-(3,5-Difluoropyridin-2-yl)ethyl]-2-methylpropane-2-sulfinamide


N-[(1E)-(3,5-Difluoropyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide (Intermediate 20, 2.5 g, 9.6 mmol) was dissolved in anhydrous TBME (40 mL) and cooled to -78°C. The resulting solution was treated drop-wise with MeMgBr solution (6.4 mL of 3M in Et₂O, 19.2 mmol) at -78°C under nitrogen atmosphere. After stirring for 2 hours at -78°C, the reaction mixture was quenched with saturated NH₄Cl (aq) solution and warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried over Na₂SO₄ and concentrated. Purification by column chromatography (Hexanes: EtOAc = 1:1) provided the title compound (2.0 g, 78%) as a slightly yellow oil.

LC-MS: 263 [M+H].

Intermediate 22
N-[Cyclopropyl(5-fluoropyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide, hydrochloride salt
Following a procedure similar to the one used for the synthesis of Intermediate 3, the title salt was synthesized from N-[(5-fluoropyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide (Intermediate 21) and cyclopropylmagnesium bromide.

LC-MS: 271 [M+H].

Intermediate 23
(S)-1-Cyclopropyl-1-(5-fluoropyridin-2-yl)methanamine, hydrochloride salt
Following a similar procedure to that of Intermediate 26, the title salt was synthesized from N-[cyclopropyl(5-fluoropyridin-2-yl)methyl]-2-methylpropane-2-sulfinamide, hydrochloride salt (Intermediate 22). LC-MS: 167 [M+H].

Intermediate 24
(RS)-N-[(1R)-[(tert-butyl(dimethyl)silyl]oxy] ethylidene]-2-methylpropane-2-sulfinamide
To a solution of (1R)-2-methylpropane-2-sulfinamide (2.5 g, 20.6 mmol) and [(tert-butyl(dimethyl)silyl]oxy}acetaldehyde (4.32 ml, 22.7 mmol) in CH₂Cl₂ (30 ml) was added anhydrous CuSO₄ (7.23 g, 45.32 mmol). The reaction mixture was stirred at room temperature for 2 days. The mixture was filtered through Celite®, washed with CH₂Cl₂ and concentrated in vacuo. Purification by column chromatography (Biotage, 0-30% EtOAc in hexanes) provided
the title compound.

^1^H NMR (CDCl\textsubscript{3}) 5 7.86 - 8.24 (m, 1 H) 4.53 (d, 2 H) 1.15 - 1.23 (m, 9 H) 0.90 (s, 9 H) 0.08 (s, 6 H).

5 **Intermediate 25**

\((\text{S})-\text{N-(i?)-2-\text{[(tert-Butyl(dimethyl)silyloxy]-l-(5-fluoropyridin-2-yl)ethenyl]-2-methylpropane-2-sulfanamide}}^*\)

To a cold solution of 2-bromo-5-fluoropyridine (1.3 g, 7.2 mmol) in Et\textsubscript{2}O (8 ml) at -68 °C was added a solution of t-BuLi (1.7 M in pentane, 8.5 ml, 14.4 mmol) with caution. The temperature of the mixture was kept below -65 °C and the mixture was allowed to stir for 15 minutes at -70°C. To a cooled solution (-75 °C) of (i?)-N-(2-\{[(tert-buty])-dimethyl)silyl]oxy\}ethylidene)-2-methylpropane-2-sulf \text{Ê}n{	extilde}{\text{amide}} (**Intermediate 24**, 1.0 g, 3.6 mmol) in Et\textsubscript{2}O (24 ml) was cannulated a solution of the above lithium compound over 15 minutes. The mixture was allowed to stir at -78 °C for 3 hours whereupon saturated NH\textsubscript{4}Cl solution was added. The mixture was diluted with EtOAc and the organic layer was washed with brine and concentrated. Column chromatography (Biotage, 20-40% EtOAc/hexanes) gave the title compound as a solid (higher \text{Rf} on TLC, 1.19 g) together with the lower \text{Rf} on TLC, 166 mg). ^1^H NMR (CDCl\textsubscript{3}) \(\delta\) 8.41 (s, 1 H) 7.35 (d, 2 H) 4.59 (t, 1 H) 4.43 (d, 1 H) 3.82 - 4.02 (m, 2 H) 1.23 (s, 9 H) 0.81 (s, 9 H) -0.06 (d, 6 H).

* \text{Rf} is intended to indicate that the stereo configuration of sulfur is \text{R}.

5 **Intermediate 26**

(2i?)-2-Amino-2-(5-fluoropyridin-2-yl)ethanol hydrochloride salt

To a solution of (i?)-2-\{[(tert-butyl(dimethyl)silyl]oxy\}-l-(5-fluoropyridin-2-yl)ethyl]-

2-methylpropane-2-sulf \text{Ê}n{	extilde}{\text{amide}} (**Intermediate 25**, 1.13 g, 3.02 mmol) in MeOH (15 ml) was added HCl (4 M in dioxane, 3.02 ml, 12.08 mol) at 0°C and the mixture was stirred for 15 minutes and then concentrated. The mixture was triturated from hexanes, providing the title salt (575 mg).

^1^H NMR \(\delta\) 8.62 (s, 1 H) 8.55 (s, 2 H) 7.76 - 7.93 (m, 1 H) 7.65 (dd, 1 H) 4.43 (d, 1 H) 3.77 (s, 2 H).
**Intermediate 27**

3,5-Difluoro-2-hydrazinylpyridine

In a 250 mL round-bottomed flask was added hydrazine monohydrate (17.69 mL, 563.61 mmol) and 2,3,5-trifluoropyridine (25.0 g, 187.87 mmol) in THF (150 mL) to give a colorless solution. The reaction was stirred for 72 hours at 50 °C. Concentration removed THF, and EtOAc (80 mL) was added. Filtration afforded the first crop of product as a solid which was washed with water (50 mL). The aqueous layer was extracted with EtOAc (3 X 30 mL). Concentration of the combined organic layers afforded the second crop of the product. The crude product was purified by silica gel chromatography and eluted with EtOAc/hexane (30%). The collected fractions were concentrated to give the title compound (23.0 g, 84% yield).

1H NMR δ 4.09 (s, 2 H), 7.62 (ddd, 1 H), 7.75 (s, 1 H), 7.96 (d, 1 H).

**Intermediate 28**

2-Bromo-3,5-difluoropyridine

To a 500 mL round-bottomed flask was added 3,5-difluoro-2-hydrazinylpyridine (Intermediate 27, 16.0 g, 110.26 mmol) in CHCl3 (158 mL) to give a brown suspension. The reaction mixture was heated to 40 °C, and bromine (14.20 ml, 275.65 mmol) was added drop-wise over 15 minutes. The reaction mixture was refluxed at 60 °C for 1 hour. After cooling down to room temperature, the flask was placed in a ice bath, and sat. NaHCO3 was added very slowly to quench the reaction. The reaction mixture was extracted with DCM (2 X 80 mL), dried over Na2SO4, and concentrated, providing the crude product. The crude product was purified using a silica gel column and was eluted with EtOAc/hexane (0-20%). The collected fractions were concentrated to give the title compound (12.0 g, 56% yield).

1H NMR δ 8.18 (td, 1 H), 8.46 (d, 1 H).

**Intermediate 29**

2-Bromo-3,5-difluoro-4-(trimethylsilyl)pyridine

To a 250 mL round-bottomed flask was added 2-bromo-3,5-difluoropyridine (Intermediate 28, 5.35 g, 27.58 mmol) in THF (55.2 ml), giving a yellow solution. The solution was cooled to -78 °C and LDA (22.98 ml, 41.37 mmol) was added. The solution turned dark immediately, and after stirring at room temperature for 10 minutes, chlorotrimethylsilane (3.66 ml, 28.96 mmol) was
added. After 30 minutes, sat. NH₄Cl was added to quench the reaction. The reaction mixture was extracted with EtOAc (2 X 30 mL), dried over Na₂SO₄, and concentrated, providing the crude product. The crude product was purified with a silica gel column, and was eluted with EtOAc/hexane (0-20%). The collected fractions were concentrated to give the title compound (5.90 g, 80% yield).

¹H NMR δ 0.40 (s, 9 H), 8.34 (s, 1 H).

**Intermediate 30**

N-(2-(fer?Butyldimethylsilyloxy)-1-(3,5-difluoro-4-(trimethylsilyl)pyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide

In a 250 mL round-bottomed flask was 2-bromo-3,5-difluoro-4-(trimethylsilyl)pyridine (Intermediate 29, 5.9 g, 22.17 mmol) in THF (36.9 ml) to give a yellow solution. The solution was cooled to -78 °C, and BuLi (13.85 ml, 22.17 mmol) was added. After stirring at that temperature for 10 min, (E)-N-(2-(fer?Butyldimethylsilyloxy)ethylidene)-2-methylpropane-2-sulfanamide (Intermediate 10, 7.38 g, 26.60 mmol) was added. The reaction was stirred for another 20 minutes, and saturated NH₄Cl (40 mL) was added to quench the reaction. The reaction mixture was warmed up to room temperature, and extracted with EtOAc (2 x 20 mL). The organic layer was dried over Na₂SO₄, and concentrated to give the crude product. The crude product was purified with a silica gel column and was eluted with EtOAC/hexane (0-60%). The collected fractions were concentrated to give the title compound (5.0 g, 48.5% yield).

¹H NMR δ -0.17 (s, 3 H), -0.06 (s, 3 H), 0.37 (s, 9 H), 0.71 (s, 9 H), 1.05 (s, 9 H), 3.92 (m, 2 H), 4.67 (m, 1 H), 5.50 (d, J = 7.91 Hz, 1 H), 8.44 (s, 1 H).

The title compound may also be prepared by the following procedure:

To a 500 mL round-bottomed flask was added 3,5-difluoropyridine (4.22 g, 36.67 mmol) in tetrahydrofuran (147 ml), giving a colorless solution. The solution was cooled to -78 °C before LDA (20.37 ml, 36.67 mmol) was added. After stirring at -78 °C for 10 minutes, chlorotrimethylsilane (4.64 ml, 36.67 mmol) was added slowly. The reaction mixture was kept at -78 °C for another 10 minutes, LDA (50.9 ml, 91.67 mmol) was slowly added, and the mixture was allowed to stir for 30 minutes before (R)-(E)-N-(2-(fer?Butyldimethylsilyloxy)ethylidene)-2-
methylpropane-2-sulfinamide (10.18 g, 36.67 mmol) was added in THF (20 mL). Sat. NH₄Cl (80 mL) was added to quench the reaction after 30 minutes. The reaction mixture was extracted with EtOAc (2 X 50 mL), drying (Na₂SO₄), and concentration gave the crude product. The crude product was purified with a silica gel column and was eluted with EtOAc/hexane (0-40%). The collected fractions were concentrated to give the title compound (41.1%).

Intermediate 31

**tert-Butyl 1-(3,5-difluoropyridin-2-yl)-2-hydroxyethylcarbamate**

To a 200 mL round-bottomed flask was added N-(2-(tert-butylidemthysilyloxy)-l-(3,5-difluoro-4-(trimethylsilyl)pyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide (Intermediate 30, 5.0 g, 10.76 mmol) in methanol (45 ml), giving a brown solution. The solution was cooled to 0°C, and HCl (4 M in dioxane) (10.76 ml, 43.03 mmol) was added. The reaction mixture was stirred at 0°C for 1 hour. The reaction mixture was concentrated in a 250 mL of round-bottomed flask to give a residue (2.65 g). To the residue was added water (35 mL), giving a yellow solution. The yellow solution was diluted with THF (70 mL). At rt, BoC₂O (3.00 mL, 12.91 mmol) and NaOH (8.61 mL, 5 M aq solution) were added. The reaction was allowed to stir at rt for 1 hour. Extraction with EtOAc (2 X 40 mL), drying (Na₂SO₄), and concentration gave the crude product. The crude product was loaded into a silica gel chromatography and eluted with EtOAc/hexane (20-80%). Collected fractions were concentrated to give the product (1.80 g, 61% yield). LCMS (M + Na) = 297.

Intermediate 32

**tert-Butyl 1-(3,5-difluoropyridin-2-yl)-2-methoxyethylcarbamate**

In a 200 mL round-bottomed flask was added tert-butyl 1-(3,5-difluoropyridin-2-yl)-2-hydroxyethylcarbamate (Intermediate 31, 1.80 g, 6.60 mmol) in THF (25 mL), giving a brown solution. The solution was cooled to -15°C using NaCl ice bath. Potassium tert-butoxide (1.481 g, 13.2 mmol) was added. The reaction mixture was kept at that temperature, and after 20 minutes iodomethane (0.413 mL, 6.6 mmol) was added. The reaction was stirred at that temperature for 1.5 hours. Monitoring by TLC showed some starting material left, so an additional 0.3 g of potassium tert-butoxide was added, followed by 0.05 mL of iodomethane. After another 10 minutes, sat. NH₄Cl was added to work up the reaction. The reaction mixture
was extracted (EtOAc, 2 X 15 mL), dried over Na₂SO₄, and concentrated, giving the crude product. The crude product was added to a silica gel column and eluted with EtOAC/hexane (0-40%). The collected fractions were concentrated to give the title compound (1.0 g, 53%).

\[ ^1H \text{NMR} \delta 1.34 (s, 9 H), 3.21 (s, 3 H), 3.57 (d, 2 H), 5.06 (d, 1 H), 7.28 (d, 1 H), 7.90 (m, 1 H), 8.49 (m, 1 H). \]

**Intermediate 33**

1-(3,5-Difluoropyridin-2-yl)-2-methoxyethanamine, hydrochloride salt

In a 100 mL round-bottomed flask was added tert-butyl 1-(3,5-difluoropyridin-2-yl)-2-methoxyethylcarbamate (Intermediate 32, 1.10 g, 3.82 mmol) in MeOH (5.0 mL), giving a colorless solution. HCl in dioxane (1.908 mL, 7.63 mmol) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 2 hours. Concentration removed MeOH, and dry ether (10 mL) was added to the residue. Decanting removed the ether, and concentration gave the title salt as a solid (0.7 g, 97%).

\[ ^1H \text{NMR} \delta 3.29 (s, 3 H), 3.72 (m, 2 H), 4.83 (s, 1 H), 8.13 (m, 1 H), 8.65 (m, 3 H). \]

**Intermediate 34**

5-Fluoro-2-vinylpyrimidine

To a stirred solution of potassium vinyltrifluoroborate (9.80 g, 73.19 mmol), 2-chloro-5-fluoropyrimidine (9.32 mL, 73.19 mmol), PPh₃ (2.304 g, 8.78 mmol), and Cs₂CO₃ (71.5 g, 219.58 mmol) in THF (144 mL) and water (16 mL) was added PdCl₂ (0.519 g, 2.93 mmol) in one portion. The reaction mixture was heated to 85 °C for 48 hours. After cooling, the reaction mixture was filtered through celite with the aid of DCM (100mL). The solids that remained in the flask were triturated with DCM and filtered. The resulting filtrate was carefully concentrated to give 5-fluoro-2-vinylpyrimidine as a heterogeneous brown oil, which was used directly in the next step.

\[ ^1H \text{NMR} (400 MHz, CDCl₃) \delta 5.70 (d, 1 H) 6.53 (dd, 1 H) 6.86 (dd, 1 H) 8.55 (s, 2 H); LCMS: [M+H] = 124.36. \]

**Intermediate 35**

5-Fluoro-2-(oxiran-2-yl)pyrimidine
To a stirred solution of 5-fluoro-2-vinylpyrimidine (Intermediate 34, 9.06 g, 73 mmol), (S,S)-(+) N,N’-Bis(3,5-di- tert-butylsalicylidene)-1,2-cyclohexadiamino-manganese(III) chloride (0.927 g, 1.46 mmol), 4-phenylpropyl pyridine N-oxide (1.246 g, 5.84 mmol), sodium phosphate, dibasic (1.036 g, 7.30 mmol) in water (76 ml) and DCM (106 ml), was added NaOCl solution (291 mg, 1.97 mmol) in one portion. The reaction was monitored by TLC. The reaction proceeded to 60% conversion, then the reaction was filtered through celite with the aid of DCM. The aqueous layer was extracted with DCM. The combined organic extracts were dried over Na₂SO₄ and concentrated. Purification via ISCO chromatography (0% to 10% to 20% EtOAc-hexanes, DCM load, SiO₂) gave the title compound (2.80 g, 27.4 %) as a yellow oil.

**Intermediate 36**

2-Azido-l-(5-fluoropyrimidin-2-yl)ethanol

To a stirred solution of 5-fluoro-2-(oxiran-2-yl)pyrimidine (Intermediate 35, 2.8 g, 19.98 mmol) and ammonium chloride (1.817 g, 33.97 mmol) in MeOH (200 mL) was added NaN₃ (3.25 g, 49.96 mmol) in one portion. The reaction mixture was heated to 50 oC for 8 hours. After cooling, the MeOH was removed via rotary evaporation and the resulting solids were partitioned between EtOAc and brine. The aqueous phase was extracted with EtOAc and the combined organic layers were dried over Na₂SO₄ and concentrated. Purification via ISCO chromatography (0% to 23% to 50% EtOAc-hexanes, DCM load, SiO₂) gave the title compound (0.500 g, 13.66 %) and 2-azido-l-(5-fluoropyrimidin-2-yl)ethanol (1.600 g, 43.7 %) as yellow oils. ¹H NMR (400 MHz, CDCl₃) δ 3.02 (t, 1 H) 4.07 (t, 2 H) 4.74 (t, 1 H) 8.64 (s, 2 H); LCMS: [M+H] = 154.42.

**Intermediate 37**

2-(l-Azido-2-methoxyethyl)-5-fluoropyrimidine

To a stirred solution of 2-azido-2-(5-fluoropyrimidin-2-yl)ethanol (Intermediate 36, 360 mg, 1.97 mmol) and a proton-sponge (1.8-Bis-(dimethylamino)-naphthalene) (421 mg, 1.97 mmol) in DCM (19 ml) at 0 oC was added trimethyloxonium tetrafluoroborate (291 mg, 1.97 mmol) in one portion. The reaction was monitored by TLC. The reaction proceeded to 60% conversion, then
stalled. Additional proton-sponge (1,8-Bis-(dimethylamino)-naphthalene) (21.1 mg, 0.98 mmol) and Trimethyloxonium tetrafluoroborate (116 mg, 0.79 mmol) were added. The reaction reached 85% conversion. Water was added and the reaction mixture was partitioned between EtOAc and 0.5 M (aq) CuSO₄ to give a partial emulsion. This biphasic mixture was filtered through a fritted funnel with the aid of EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organics were dried over Na₂SO₄ and concentrated.

Purification via ISCO chromatography (0% to 10% to 20% EtOAc-hexanes, DCM load, SiO₂) gave the title compound (243 mg, 62.7%) as a colorless oil.

1H NMR (400 MHz, CDCl₃) δ 3.41 (s, 3 H) 3.85 - 3.94 (m, 2 H) 4.80 (dd, 1 H) 8.62 (s, 2 H); LCMS: [M+H] = 198.01.

Intermediate 38

1-(5-Fluoropyrimidin-2-yl)-2-methoxyethanamine

To a stirred solution of 2-(1-azido-2-methoxyethyl)-5-fluoropyrimidine (Intermediate 37, 243 mg, 1.23 mmol) in THF (10.6 mL) and water (1.767 mL) was added 4-diphenylphosphino polystyrene resin (998 mg, 1.85 mmol) in one portion. The reaction mixture was heated to 65°C for 2 hours. After cooling, the reaction mixture was filtered with the aid of EtOAc and concentrated to give the title compound (196 mg, 93%) as a yellow oil which was used without further purification.

1H NMR (400 MHz, CDCl₃) δ 3.35 (s, 3 H) 3.64 (dd, 1 H) 3.76 (dd, 1 H) 4.34 (dd, 1 H) 8.57 (s, 2 H); LCMS: [M+H] = 171.82.

Example 1

5-Chloro-\(\text{N}^2\)-[(15)-l-(5-fluoropyridin-2-yl)propyll- \(\text{N}^4\)-(5-methyl-1 \text{H}-pyrazol-3-yl)pyrimidine-2,4-diamine\]
A mixture of 2,5-dichloro-\(N\)-(5-methyl-1\(H\)-pyrazol-3-yl)pyrimidin-4-amine (Intermediate 4, 1 eq.), [(15)-1-(5-fluoropyridin-2-yl)propyl]amine, hydrochloride salt (Intermediate 3, 1 eq.), and DIPEA (2 eq.) in n-BuOH was charged into a microwave reaction vessel. The vessel was sealed and heated in a microwave reactor at 180 °C for 6 hours. Solvent was removed under reduced pressure and the residue was purified by Gilson (10-50% ACN/H2O, 15 minutes) providing the title compound.

LC-MS: 362 [M+1].

\(^{1}\text{H} \text{NMR} \ \delta 8.50 \ (s, \ 1 \text{ H}) \ 7.90 \ (d, \ 1 \text{ H}) \ 7.59 \ - \ 7.78 \ (m, \ 2 \text{ H}) \ 7.41 \ (s, \ 1 \text{ H}) \ 5.97 \ (s, \ 1 \text{ H}) \ 4.84 \ (d, \ 1 \text{ H}) \ 2.16 \ - \ 2.23 \ (s, \ 3 \text{ H}) \ 1.71 \ - \ 1.92 \ (m, \ 2 \text{ H}) \ 0.88 \ (t, \ 3 \text{ H}).

**Example 2**

3-((5-Chloro-4-\(N\)-(5-methyl-1\(H\)-pyrazol-3-yl)amino)pyrimidin-2-yliamino)-3-(5-fluoropyridin-2-yl)-\(N\)-methylpropanamide

2,5-Dichloro-\(N\)-(5-methyl-1\(H\)-pyrazol-3-yl)pyrimidin-4-amine (Intermediate 4) and 3-amino-3-
(5-fluoropyridin-2-yl)-N-methylpropanamide, hydrochloride salt (Intermediate 9) were reacted using a procedure similar to the one described for the synthesis of Example 1, providing the title compound as a mixture of enantiomers.

LC-MS: 405 [M+1]. $^1$H NMR  $\delta$ 9.97 (br.s, 1 H) 9.41 (br.s, 1 H) 8.55 (s, 1 H) 8.38 (s, 1 H) 8.18 (s, 1 H) 8.01 (br.s, 1 H) 7.85 (s, 1 H) 7.68 (s, 1 H) 7.38 (s, 1 H) 6.36 (br.s, 1 H) 6.00 (s, 1 H) 5.24 - 5.49 (m, 1 H) 2.63 - 2.82.

**Column and solvent conditions**
The R and S enantiomers of the title compound were chirally separated using a Berger AutoPrep SFC Chiral Purification system.

- **Column type, particle size:** Chiralpak AS-H, 5µ
- **Column dimensions (mm):** 250 x 21
- **Modifier / additive:** 40% isopropanol / 0.1% dimethyl ethylamine
- **Flow rate (ml/min):** 60
- **Oven (°C):** 40
- **Outlet Pressure (bar):** 100

**Post purification purity check**
Sample purity was checked with a chiral SFC (Berger SFC) using a Diode Array.

- **Column type, particle size:** Chiralpak AS-H, 5µ
- **Column dimensions (mm):** 250 x 4.6
- **Modifier / additive:** 40% isopropanol / 0.1% dimethyl ethylamine
- **Flow rate (ml/min):** 2.5
- **Oven (°C):** 35
- **Outlet Pressure (bar):** 120

**Example 2(a). First Eluting Compound**
3-({5-Chloro-4-[(5-methyl-1 $H$-pyrazol-3-yl)aminolpyrimidin-2-yl]amino)-3-(5-fluoropyridin-2-yl)-N-methylpropanamide, enantiomer A

The first eluting compound had a retention time of 2.6 minutes.
LC-MS: 405 [M+H]. $^1$HNMR $\delta$ 9.97 (br.s, 1 H) 9.41 (br.s, 1 H) 8.55 (s, 1 H) 8.38 (s, 1 H) 8.18 (s, 1 H) 8.01 (br.s, 1 H) 7.85 (s, 1 H) 7.68 (s, 1 H) 7.38 (s, 1 H) 6.36 (br.s, 1 H) 6.00 (s, 1 H) 5.24 - 5.49 (m, 1 H) 2.63 - 2.82.

5 Example 2(b), Second Eluting Compound
3-(5-Chloro-4-[(5-methyl-l $H$-pyrazol-3-yl)aminopyrimidin-2-yUamino)-3-(5-fluoropyridin-2-yl)-N-methylpropanamide. enantiomer B

The second eluting compound had a retention time of 4.9 minutes.
LC-MS: 405 [M+H]. $^1$HNMR $\delta$ 9.97 (br.s, 1 H) 9.41 (br.s, 1 H) 8.55 (s, 1 H) 8.38 (s, 1 H) 8.18 (s, 1 H) 8.01 (br.s, 1 H) 7.85 (s, 1 H) 7.68 (s, 1 H) 7.38 (s, 1 H) 6.36 (br.s, 1 H) 6.00 (s, 1 H) 5.24 - 5.49 (m, 1 H) 2.63 - 2.82.

Enantiomeric excess (e.e.) for each enantiomer of Example 2 was >98 %, using area percent at 254 nm.

15 Example 3
5-Chloro-$N^2$-[1-(5-fluoropyridin-2-yl)-2-methoxyethyl]- $N^4$-(5-methyl-l $H$-pyrazol-3-yl)pyrimidine-2,4-diamine

![Chemical Structure](image)

20 2,5-Dichloro- $N$-(5-methyl-l $H$-pyrazol-3-yl)pyrimidin-4-amine (Intermediate 4) and 1-(5-fluoropyridin-2-yl)-2-methoxyethanamine, hydrochloride salt (Intermediate 13) were reacted using a procedure similar to the one described for the synthesis of Example 1, providing the title compound as a mixture of enantiomers.

LC-MS: 378 [M+H]. $^1$HNMR $\delta$ 9.95 (s, 1 H) 9.43 (s, 1 H) 8.56 (s, 1 H) 8.35 (s, 1 H) 8.18 (s, 1
Column and solvent conditions

The R and S enantiomers of the title compound were chirally separated using a Berger AutoPrep SFC Chiral Purification system.

Column type, particle size: Chiralpak AD-H, 5µ
Column dimensions (mm): 250 x 21
Modifier / additive: 50% methanol / 0.1% dimethyl ethylamine
Flow rate (ml/min): 60
Oven (ºC): 40
Outlet Pressure (bar): 100

Post purification purity check

Sample purity was checked with a chiral SFC (Berger SFC) using a Diode Array.

Column type, particle size: Chiralpak AD-H, 5µ
Column dimensions (mm): 100 x 4.6
Modifier / additive: 50% methanol / 0.1% dimethyl ethylamine
Flow rate (ml/min): 5
Oven (ºC): 35
Outlet Pressure (bar): 120

Example 3(a), First Eluting Compound

5-Chloro-4-(l-(5-fluoropyridin-2-yl)-2-methoxyethyl)- N4-(5-methyl-lH-pyrazol-3-y1)pyrimidine-2,4-diamine, enantiomer A

The first eluting compound had a retention time of 0.8 minutes.
LC-MS: 378 [M+l]. 1H NMR δ 9.95 (s, 1 H) 9.43 (s, 1 H) 8.56 (s, 1 H) 8.35 (s, 1 H) 8.18 (s, 1 H) 7.97 (s, 1 H) 7.70 (t, 1 H) 7.37 - 7.56 (m, 1 H) 6.36 (s, 1 H) 5.90 (s, 1 H) 4.98 - 5.34 (m, 1 H) 3.62 - 3.81 (m, 1 H) 3.24 (s, 3 H) 2.21 (s, 3 H).

Example 3(b), Second Eluting Compound
5-Chloro-\(N^2\)-[1-(5-fluoropyridin-2-yl)-2-methoxyethyl]-\(N^4\)-(5-methyl-1 \(H\)-pyrazol-3-yl)pyrimidine-2,4-diamine, enantiomer B

The second eluting compound had a retention time of 1.7 minutes.

LC-MS: 378 [M+1]. \(1^H\) NMR \(\delta\) 9.95 (s, 1 H) 9.43 (s, 1 H) 8.56 (s, 1 H) 8.35 (s, 1 H) 8.18 (s, 1 H) 7.97 (s, 1 H) 7.70 (t, 1 H) 7.37 - 7.56 (m, 1 H) 6.36 (s, 1 H) 5.90 (s, 1 H) 4.98 - 5.34 (m, 1 H) 3.62 - 3.81 (m, 1 H) 3.24 (s, 3 H) 2.21 (s, 3 H).

Enantiomeric excess (e.e.) for each enantiomer of Example 3 was >98 %, using area percent at 254 nm.

Example 4

5-Fluoro-\(N^2\)-[1-(5-fluoropyridin-2-yl)-2-methoxyethyl]-\(N^4\)-(5-methyl-1 \(H\)-pyrazol-3-yl)pyrimidine-2,4-diamine

\[
\text{\begin{align*}
\text{F} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{N} & \quad \text{H-N} \\
\text{O} & \quad \text{O} \\
\text{F} & \quad \text{F}
\end{align*}}
\]

2-Chloro-5-fluoro-\(N\)-(5-methyl-1 \(H\)-pyrazol-3-yl)pyrimidin-4-amine (Intermediate 14) and 1-(5-fluoropyridin-2-yl)-2-methoxyethanamine, hydrochloride salt (Intermediate 13) were reacted using a procedure similar to the one described for the synthesis of Example 1, providing the title compound as a mixture of enantiomers.

LC-MS: 362 [M+1]. \(1^H\) NMR (MeOD) \(\delta\) 2.18 (s, 3 H) 3.67 (s, 3 H) 5.04 - 5.32 (m, 2 H) 5.61 - 5.88 (m, 1 H) 6.14 (s, 1 H) 7.38 - 7.64 (m, 2 H) 7.79 (s, 1 H) 8.46 (s, 1 H).

Column and solvent conditions

The R and S enantiomers of the title compound were chirally separated using a Berger AutoPrep SFC Chiral Purification system.
Column type, particle size: Chiralpak AD-H, 5µ
Column dimensions (mm): 250 x 21
Modifier / additive: 40% methanol
Flow rate (ml/min): 60
Oven (°C): 40
Outlet Pressure (bar): 100

Example 4(a), First Eluting Compound

5-Fluoro-\(\text{N}^2\)-[\(l\)-(5-fluoropyridin-2-yl)-2-methoxyethyl]-\(\text{N}^4\)-(5-methyl-1\text{H}-pyrazol-3-yl)pyrimidine-2,4-diamine. enantiomer A
The first eluting compound had a retention time of 3.7 minutes.
LC-MS: 362 [M+1]. \(^1\)H NMR (MeOD) \(\delta\) 2.18 (s, 3 H) 3.67 (s, 3 H) 5.04 - 5.32 (m, 2 H) 5.61 - 5.88 (m, 1 H) 6.14 (s, 1 H) 7.38 - 7.64 (m, 2 H) 7.79 (s, 1 H) 8.46 (s, 1 H).

Example 4(b), Second Eluting Compound

5-Fluoro-\(\text{N}^2\)-[\(l\)-(5-fluoropyridin-2-yl)-2-methoxyethyl]-\(\text{N}^4\)-(5-methyl-1\text{H}-pyrazol-3-yl)pyrimidine-2,4-diamine. enantiomer B
The second eluting compound had a retention time of 6.0 minutes.
LC-MS: 362 [M+1]. \(^1\)H NMR (MeOD) \(\delta\) 2.18 (s, 3 H) 3.67 (s, 3 H) 5.04 - 5.32 (m, 2 H) 5.61 - 5.88 (m, 1 H) 6.14 (s, 1 H) 7.38 - 7.64 (m, 2 H) 7.79 (s, 1 H) 8.46 (s, 1 H).

Example 5

5-Fluoro-\(\text{N}^2\)-[\(l\)S]-[\(l\)-(5-fluoropyridin-2-yl)propyl]-\(\text{N}^4\)-(5-methyl-1\text{H}-pyrazol-3-yl)pyrimidine -2,4-diamine
2-Chloro-5-fluoro- \textit{N}-(5-methyl-1 \textit{H}-pyrazol-3-yl)pyrimidin-4-amine \textbf{(Intermediate 14)} and [(15)-1-(5-fluoropyridin-2-yl)propyl]amine, hydrochloride salt \textbf{(Intermediate 3)} were reacted using a procedure similar to the one described for the synthesis of \textbf{Example 1}, providing the title compound.

LC-MS: 346 [M+H]. \textsuperscript{1}H NMR \(\delta 0.90 \text{ (m, 3H)}\) 1.76 \(\text{ (m, 2H)}\) 2.18 \(\text{ (s, 3H)}\) 4.81 \(\text{ (br, IH)}\) 6.12 \(\text{ (br, IH)}\) 7.23 \(\text{ (br, IH)}\) 7.42 \(\text{ (s, IH)}\) 7.81 \(\text{ (s, IH)}\) 8.47 \(\text{ (s, IH)}\) 9.47 \(\text{ (br, IH)}\).

\textbf{Example 6}

3-\{\textit{N}-(5-chloro-4-\textit{H}-pyrazol-3-yl)aminolpyrimidin-2-yUamino\}-3-(5-fluoropyridin-2-y)propan-1-ol

2,5-Dichloro- \textit{N}-(5-methyl-1 \textit{H}-pyrazol-3-yl)pyrimidin-4-amine \textbf{(Intermediate 4)} and 3-amino-3-(5-fluoropyridin-2-yl)propan-1-ol, hydrochloride salt \textbf{(Intermediate 16)} were reacted using a procedure similar to the one described for the synthesis of \textbf{Example 1}, providing the title compound as a mixture of enantiomers.
LC-MS: 378 [M+1]. \(^1\)H NMR \(\delta\) 1.82 - 2.08 (m, 1 H) 2.16 (s, 3 H) 2.27 - 2.39 (m, 1 H) 3.45 (m, 1 H) 4.27 - 4.56 (m, 1 H) 4.99 - 5.17 (m, 1 H) 5.97 (s, 1 H) 7.25 - 7.44 (m, 1 H) 7.55 - 7.86 (m, 1 H) 8.03 (s, 1 H) 8.25 (s, 1 H) 8.56 (s, 1 H).

5 Column and solvent conditions
The R and S enantiomers of the title compound were chirally separated using a Berger AutoPrep SFC Chiral Purification system.

Column type, particle size: Chiralpak AD-H, 5\(\mu\)
Column dimensions (mm): 250 x 21
Modifier / additive: 40\% methanol
Flow rate (ml/min): 60
Oven (\(^\circ\)C): 40
Outlet Pressure (bar): 100

15 Post purification purity check
Sample purity was checked with a chiral SFC (Berger SFC) using Diode Array.

Column type, particle size: Chiralpak AD-H, 5\(\mu\)
Column dimensions (mm): 100 x 4.6
Modifier / additive: 40\% methanol
Flow rate (ml/min): 5
Oven (\(^\circ\)C): 35
Outlet Pressure (bar): 120

Example 6(a). First Eluting Compound
3-({5-Chloro-4-[(5-methyl-1 \(^5\)H-pyrazol-3-yl)aminopyrimidin-2-yUamino)-3-(5-fluoropyridin-2-yl)propan-1-ol,  enaniomer A
The first eluting compound had a retention time of 0.8 minutes, and had an enantiomeric excess of>98%.

LC-MS: 378 [M+1]. \(^1\)H NMR \(\delta\) 1.82 - 2.08 (m, 1 H) 2.16 (s, 3 H) 2.27 - 2.39 (m, 1 H) 3.45 (m, 1 H) 4.27 - 4.56 (m, 1 H) 4.99 - 5.17 (m, 1 H) 5.97 (s, 1 H) 7.25 - 7.44 (m, 1 H) 7.55 - 7.86 (m, 1 H) 8.03 (s, 1 H) 8.25 (s, 1 H) 8.56 (s, 1 H).
Example 6(b), Second Eluting Compound

3-({5-Chloro-4-[{(5-methyl-1H-pyrazol-3-yl)aminolpyrimidin-2-yUamino)-3-(5-fluoropyridin-2-yl)propan-1-ol. enantiomer i3

The second eluting compound had a retention time of 1.8 minutes, and had an enantiomeric excess of 97.3%.

LC-MS: 378 [M+1]. 1H NMR δ 1.82 - 2.08 (m, 1 H) 2.16 (s, 3 H) 2.27 - 2.39 (m, 1 H) 3.45 (m, 1 H) 4.27 - 4.56 (m, 1 H) 4.99 - 5.17 (m, 1 H) 5.97 (s, 1 H) 7.25 - 7.44 (m, 1 H) 7.55 - 7.86 (m, 1 H) 8.03 (s, 1 H) 8.25 (s, 1 H) 8.56 (s, 1 H).

Enantiomeric excess for each enantiomer of Example 6 was calculated using area percent at 254 nm.

Example 7

S-Chloro-^-cyclopropylKS-fluoropyridin^-yDmethyl-^-fS-methyl-1H-pyrazol-S-yl)pyrimidine-2,4-diamine

2,5-Dichloro- N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine (Intermediate 4) and (S)-I-
Cyclopropyl-I-(5-fluoropyridin-2-yl)methanamine, hydrochloride salt (Intermediate 23) were reacted using a procedure similar to the one described for the synthesis of Example 1, providing the title compound.

LC-MS: 374 [M+1]. 1H NMR δ 0.27 - 0.74 (m, 4 H) 1.29 (dd, 1 H) 2.28 (s, 3 H) 4.19 - 4.48 (m, 1 H) 5.97 (s, 1 H) 7.46 (s, 1 H) 7.60 - 7.95 (m, 1 H) 8.22 (s, 1 H) 8.54 (s, 1 H) 8.89 (s, 1 H) 10.21
Example 8

(2i?-V2-((5-Chloro-4-[(5-methyl-lH-pyrazol-3-yl)amino]pyrimidin-2-yl)amino)-V2-(5-fluoropyridin-2-yl)ethanol, hydrochloride salt (Intermediate 26) were reacted using a procedure similar to the one described for the synthesis of Example 1, providing the title compound.

LC-MS: 364 [M+H]. 1H NMR δ 2.14 (s, 3 H) 3.69 (dd, 1 H) 4.49 (s, 1 H) 4.87 (s, 1 H) 5.77 (s, 1 H) 7.16 - 7.41 (m, 1 H) 7.52 - 7.73 (m, 1 H) 8.15 (s, 1 H) 8.54 (s, 1 H).

Example 9

In a 200 mL round-bottomed flask was added 2,5-dichloro-N-(5-methyl-lH-pyrazol-3-yl)pyrimidin-4-amine (Intermediate 4) and (2i?-2-amino-2-(5-fluoropyridin-2-yl)ethanol, hydrochloride salt (Intermediate 26) were reacted using a procedure similar to the one described for the synthesis of Example 1, providing the title compound.
yl)pyrimidin-4-amine (Intermediate 4, 0.710 g, 2.91 mmol) chloride in 3-methyl-butanol (26.4 ml) to give a colorless solution. l-(3,5-difluoropyridin-2-yl)-2-methoxyethanamine, hydrochloride salt (Intermediate 33, 0.500 g, 2.64 mmol) and DIPEA (1.385 ml, 7.93 mmol) were added. The reaction was refluxed at 150 °C for 24 hours. The solvent was removed under reduced pressure, and the crude product was added to a reverse phase column and was eluted with 10 mm NH4AC in H2O/CH3CN. Collected fractions were concentrated, providing the title compound as a mixture of enantiomers (0.188 g, 19% yield).

LC-MS: 396 [M + I]. 1H NMR (300 MHz, MeOD) δ 2.20 (s, 3 H), 3.23 (s, 3 H), 3.65 (m, 2 H), 5.51 (t, J = 6.03 Hz, 1 H), 6.25 (m, 1 H), 7.45 (m, 1 H), 7.79 (s, 1 H), 8.25 (d, 1 H).

Column and solvent conditions
The R and S enantiomers of the title compound were chirally separated using a Bchiral HPLC system.

Column type, particle size: Chiralpak AD, 20µ
Column dimensions (mm): 50 x 500
Modifier / additive: 80 % Hexane, 20 % Isopropanol, 0.1 % diethylamine
Flow rate (ml/min): 120

Post purification purity check
Sample purity was checked with a Chiral HPLC (Agilent 1100) using a Diode Array.

Column type, particle size: Chiralpak AD, 1µ
Column dimensions (mm): 4.6 x 250
Modifier / additive: 80 % Hexane, 20 % Isopropanol, 0.1 % diethylamine
Flow rate (ml/min): 1 ml/min

Example 9(a), First Eluting Compound
5-Chloro-N^2-(l-(3,5-difluoropyridin-2-yl)-2-methoxyethyl)-N^4-(5-methyl-lH-pyrazol-3-yl)pyrimidine-2,4-diamine, enantiomer A.

The first eluting compounds had a retention time of 13.3 minutes.

LC-MS [M + H] = 396. 1H NMR (300 MHz, MeOD) δ 2.20 (s, 3 H), 3.23 (s, 3 H), 3.65 (m, 2 H), 5.51 (t, J = 6.03 Hz, 1 H), 6.25 (m, 1 H), 7.45 (m, 1 H), 7.79 (s, 1 H), 8.25 (d, 1 H).
Example 9(b), Second Eluting Compound

5-Chloro-N²-(l-(3,5-difluoropyridin-2-yl)²-methoxyethyl)⁴-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine. enantiomer B

The second eluting compound had a retention time of 15.8 minutes, and had an enantiomeric excess of > 98%. Enantiomeric excess for the second eluting compound was calculated using area percent at 254 nm.

LC-MS [M + H] = 396. ¹H NMR (300 MHz, MeOD) δ 2.20 (s, 3 H), 3.23 (s, 3 H), 3.65 (m, 2 H), 5.51 (t, J = 6.03 Hz, 1 H), 6.25 (m, 1 H), 7.45 (m, 1 H), 7.79 (s, 1 H), 8.25 (d, 1 H).

Example 10


To a stirred solution of l-(5-fluoropyrimidin-2-yl)-2-methoxyethanamine (Intermediate 38, 200 mg, 1.17 mmol) and 2,5-dichloro-N-(5-methyl-1H-pyrazol-3-yl)pyrimidin-4-amine (Intermediate 4, 285 mg, 1.17 mmol) in butan-1-ol (5 mL) was added DIPEA (0.204 mL, 1.17 mmol) drop-wise via syringe. The reaction mixture was heated to 150 °C in a microwave for 1 hour. LCMS indicated 50% conversion. The reaction mixture was heated to 150 °C in a microwave for 4 hours. LCMS indicated 75% conversion. The reaction mixture was heated to 150 °C in a microwave for 2 hours. TLC indicated that the amine was consumed, so the reaction mixture was concentrated in vacuo. Purification via ISCO chromatography (0% to 50% to 90% EtOAc-hexanes, DCM load, SiO₂) provided the title compound as a mixture of enantiomers (250 mg, 56.5 %) in the form of a yellow oil.
LC-MS: 379 [M+H].

\[ \text{H NMR (400 MHz, MeOD)} \ \delta \ 2.21 \ (s, \ 3 \ H) \ 3.30 \ (obs, \ 3H) \ 3.83 \ (d, \ J=5.31 \ Hz, \ 2 \ H) \ 5.28 \ (t, \ J=5.18 \ Hz, \ 1 \ H) \ 6.20 \ (bs, \ IH) \ 7.80 \ (s, \ 1 \ H) \ 8.62 \ (s, \ 2 \ H). \]

5 Interval and solvent conditions

The R and S enantiomers of the title compound were chirally separated using a Berger AutoPrep SFC Chiral Purification system.

Column type, particle size: Chiralpak AD-H, 5µ
Column dimensions (mm): 21x 250

Modifier / additive: 30% Methanol / 0.4% dimethylethylamine
Flow rate (ml/min): 60
Oven (°C): 40
Outlet Pressure (bar): 100

15 Post-purification purity check

Sample purity was checked with a chiral SFC (Berger SFC) using a Diode Array.

Column type, particle size: Chiralpak AD-H, 5µ
Column dimensions (mm): 100 x 4.6
Modifier / additive: 30% Methanol
Flow rate (ml/min): 5
Oven (°C): 35
Outlet Pressure (bar): 120

Example 10(a). First Eluting Compound

5-Chloro-\(\text{N}^2\)-(l-(5-fluoropyrimidin-2-yl)-2-methoxyethyl)-7\(^V\)-(5-methyl-lH-pyrazol-3-yl)pyrimidine-2,4-diamine, enantiomer A

The first eluting compound had a retention time of 1.05 minutes.

LC-MS [M+H] = 379.16.

\[ \text{H NMR (400 MHz, MeOD)} \ \delta \ 2.21 \ (s, \ 3 \ H) \ 3.30 \ (obs, \ 3H) \ 3.83 \ (d, \ J=5.31 \ Hz, \ 2 \ H) \ 5.28 \ (t, \ J=5.18 \ Hz, \ 1 \ H) \ 6.20 \ (bs, \ IH) \ 7.80 \ (s, \ 1 \ H) \ 8.62 \ (s, \ 2 \ H). \]
Example 10(b). Second Eluting Compound

S-Chloro-$\Lambda$^-d-$\Lambda$^-S-fluoropyrimidin-$\pi$^-methoxyethyD-$\Lambda$^-fS-methyl-lH-pyrazol-$\pi$-yl]pyrimidine-2,4-diamine, enantiomer B

The second eluting compound had a retention time of 1.55 minutes.

$^1$H NMR (400 MHz, MeOD) $\delta$ 2.21 (s, 3 H) 3.30 (obs, 3H) 3.83 (d, $\omega$=5.31 Hz, 2 H) 5.28 (t, J=5.18 Hz, 1 H) 6.20 (bs, IH) 7.80 (s, 1 H) 8.62 (S, 2 H); LCMS [M+H] = 379.16.

Enantiomeric excess for each enantiomer of Example 10 was >98%, using area percent at 220 nm.
Claims

What is claimed is:

1. A compound of Formula (I):

   
   ![Formula (I)](image)

   or a pharmaceutically acceptable salt thereof, wherein

   **Ring** A is selected from pyridinyl and pyrimidinyl;

   R\(^1\) is halo;

   R\(^2\) is selected from methyl, C\(_2\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, carbocyclyl, heterocyclyl, -OR\(^2\)a, -SR\(^2\)a, -N(R\(^2\)a)\(^2\), -N(R\(^2\)a)C(O)R\(^2\)b, -N(R\(^2\)a)N(R\(^2\)a)\(^2\), -NO\(^2\), -N(R\(^2\)a)OR\(^2\)a, -ON(R\(^2\)a)\(^2\), -C(O)H, -C(O)R\(^2\)b, -C(O)\(^2\)R\(^2\)c, -C(O)N(R\(^2\)a)\(^2\), -C(O)N(R\(^2\)a)(OR\(^2\)a) -OC(O)N(R\(^2\)a)\(^2\), -N(R\(^2\)a)C(O)R\(^2\)b, -N(R\(^2\)a)C(O)N(R\(^2\)a)\(^2\), -OC(O)R\(^2\)b, -S(O)R\(^2\)b, -S(O)\(^2\)R\(^2\)b, -S(O)\(^2\)N(R\(^2\)a)\(^2\), -N(R\(^2\)a)S(O)\(^2\)R\(^2\)b, -C(R\(^2\)a)=N(R\(^2\)a), and -C(R\(^2\)a)=N(OR\(^2\)a), wherein said methyl is substituted with at least one R\(^2\)o, wherein said C\(_2\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, carbocyclyl, and heterocyclyl are optionally substituted on carbon with one or more R\(^2\)o, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R\(^2\)o;

   R\(^2\) in each occurrence is independently selected from C\(_i\)-alkyl, carbocyclyl, heterocyclyl, -C(O)H, -C(O)R\(^2\)b, -C(O)\(^2\)R\(^2\)c, -C(O)N(R\(^2\)a)\(^2\), -S(O)R\(^2\)b, -S(O)\(^2\)R\(^2\)b, -S(O)\(^2\)N(R\(^2\)a)\(^2\), -C(R\(^2\)a)=N(R\(^2\)a), and -C(R\(^2\)a)=N(OR\(^2\)a), wherein said C\(^\wedge\)alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R\(^2\)o, and wherein any -NH- moiety of said
heterocyclyl is optionally substituted with R\textsuperscript{20*};

R\textsuperscript{2a} in each occurrence is independently selected from H, Ci-alkyl, carbocyclyl, and heterocyclyl, wherein said Ci-alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R\textsuperscript{20}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R\textsuperscript{20*};

R\textsuperscript{2b} in each occurrence is independently selected from Ci-alkyl, C\textsubscript{2}\textsubscript{6}alkenyl, C\textsubscript{2}\textsubscript{6}alkynyl, carbocyclyl, and heterocyclyl, wherein said Ci-alkyl, C\textsubscript{2}-alkenyl, C\textsubscript{2}-alkynyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R\textsuperscript{20}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R\textsuperscript{20*};

R\textsuperscript{2c} in each occurrence is independently selected from Ci-alkyl, carbocyclyl, and heterocyclyl, wherein said Ci-alkyl, carbocyclyl, and heterocyclyl in each occurrence are optionally and independently substituted on carbon with one or more R\textsuperscript{20}, and wherein any -NH- moiety of said heterocyclyl is optionally substituted with R\textsuperscript{20*};

R\textsuperscript{3} is halo;

R\textsuperscript{20} in each occurrence is independently selected from halo, -CN, Ci-alkyl, C\textsubscript{2}\textsubscript{6}alkenyl, C\textsubscript{2}\textsubscript{6}alkynyl, carbocyclyl, heterocyclyl, -OR\textsuperscript{20a}, -SR\textsuperscript{20a}, -N(R\textsuperscript{20a})\textsubscript{2}, -N(R\textsuperscript{20a})C(O)R\textsuperscript{20b}, -N(R\textsuperscript{20a})N(R\textsuperscript{20a})\textsubscript{2}, -NO\textsubscript{2}, -N(R\textsuperscript{20a})-OR\textsuperscript{20a}, -O-N(R\textsuperscript{20a})\textsubscript{2}, -C(O)H, -C(O)R\textsuperscript{20b}, -C(O)\textsubscript{2}R\textsuperscript{20a}, -C(O)\textsubscript{2}N(R\textsuperscript{20a})\textsubscript{2}, -C(O)N(R\textsuperscript{20a})\textsubscript{2}, -C(O)N(R\textsuperscript{20a})(OR\textsuperscript{20a}), -OC(O)N(R\textsuperscript{20a})\textsubscript{2}, -N(R\textsuperscript{20a})C(O)\textsubscript{2}R\textsuperscript{20a}, -N(R\textsuperscript{20a})C(O)N(R\textsuperscript{20a})\textsubscript{2}, -OC(O)R\textsuperscript{20b}, -S(O)R\textsuperscript{20b}, -S(O)\textsubscript{2}R\textsuperscript{20b}, -S(O)\textsubscript{2}N(R\textsuperscript{20a})\textsubscript{2}, -N(R\textsuperscript{20a})S(O)\textsubscript{2}R\textsuperscript{20b}, -C(R\textsuperscript{20a})=N(R\textsuperscript{20a}), and -C(R\textsuperscript{20a})=N(OR\textsuperscript{20a});

R\textsuperscript{20*} in each occurrence is independently selected from Ci-alkyl, carbocyclyl, heterocyclyl, -C(O)H, -C(O)R\textsuperscript{20b}, -C(O)\textsubscript{2}R\textsuperscript{20c}, -C(O)N(R\textsuperscript{20a})\textsubscript{2}, -S(O)R\textsuperscript{20b}, -S(O)\textsubscript{2}R\textsuperscript{20b}, -S(O)\textsubscript{2}N(R\textsuperscript{20a})\textsubscript{2}, -C(R\textsuperscript{20a})=N(R\textsuperscript{20a}), and -C(R\textsuperscript{20a})=N(OR\textsuperscript{20a});

R\textsuperscript{20a} in each occurrence is independently selected from H, Ci-alkyl, carbocyclyl, and heterocyclyl;

R\textsuperscript{20b} in each occurrence is independently selected from Ci-alkyl, C\textsubscript{2}-alkenyl, C\textsubscript{2}-alkynyl, carbocyclyl, and heterocyclyl;

R\textsuperscript{20c} in each occurrence is independently selected from Ci-alkyl, carbocyclyl, and heterocyclyl;

heterocyclyl; and

n is 1 or 2.
2. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein:

R₁ is selected from methyl, C₂-6 alkyl, and carbocyclyl, wherein said methyl is substituted with at least one R₂⁰, and wherein said C₂-6 alkyl and carbocyclyl are optionally substituted on carbon with one or more R₂⁰;

R₂⁰ is selected from -OR₂⁰a and -C(O)N(R₂⁰a)₂; and

R₂⁰a is selected from H and C₁₋₆ alkyl.

3. A compound of Formula (I):

![Formula (I)](image)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from fluoro and chloro;

R² is selected from cyclopropyl, ethyl, hydroxyethyl, hydroxymethyl, methoxymethyl, and N-methylaminocarbonylmethyl; and

Ring A, R³, and n together form a group selected from 3,5-difluoropyridin-2-yl, 5-fluoropyridin-2-yl and 5-fluoropyrimidin-2-yl.

4. A compound of Formula (I) as claimed in claim 1, selected from:

S-Chloro^-CCl^-l-CS-fiuoropyridin^-yOpropyll-V-CS-methyl-1 H-pyrazol-S-y]pyrimidine -2,4-diamine ;

(35)-3-({5-Chloro-4-[5-methyl-1 H-pyrazol-3-yl]amino}pyrimidin-2-yl)amino)-3-(5-fluoropyridin-2-yl)-N-methylpropanamide;
5-Chloro-$N^2$-[(li?)-l-(5-fluoropyridin-2-yl)-2-methoxyethyl]-$N^4$-(5-methyl-lH-pyrazol-3-yl)pyrimidine -2,4-diamine;
5-Fluoro-$N^2$-[(li?)-l-(5-fluoropyridin-2-yl)-2-methoxyethyl]-$N^4$-(5-methyl-lH-pyrazol-3-yl)pyrimidine -2,4-diamine;
5-Fluoro-$N^2$-[(1S)-l-(5-fluoropyridin-2-yl)propyl]-$N^4$-(5-methyl-lH-pyrazol-3-yl)pyrimidine -2,4-diamine;
(3S)-3-((5-Chloro-4-[(5-methyl-lH-pyrazol-3-yl)amino]pyrimidin-2-yl)amino)-3-(5-fluoropyridin-2-yl)propan-1-ol;
5-Chloro-$N^2$-[(3S)-cyclopropyl(5-fluoropyridin-2-yl)methyl]-$N^4$-(5-methyl-lH-pyrazol-3-yl)pyrimidine-2,4-diamine;
(2i?)-2-((5-Chloro-4-[(5-methyl-lH-pyrazol-3-yl)amino]pyrimidin-2-yl)amino)-2-(5-fluoropyridin-2-yl)ethanol;
5-Chloro-$N^2$-[(li?)-l-(3,5-difluoropyridin-2-yl)-2-methoxyethyl]-$N^4$-(5-methyl-lH-pyrazol-3-yl)pyrimidine-2,4-diamine; and
5-Chloro-$N^2$-[(li?)-l-(5-fluoropyrimidin-2-yl)-2-methoxyethyl]-$N^4$-(5-methyl-lH-pyrazol-3-yl)pyrimidine-2,4-diamine,
or pharmaceutically acceptable salt thereof.

5. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, for use as a medicament.

6. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, in the manufacture of a medicament for the treatment of cancer.

7. A method for treating cancer in a warm-blooded animal such as man, said method comprising administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4.

8. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, for use in the treatment of cancer in a warm-blooded animal.
such as man.

9. A pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

10. A process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, said process comprising reacting a compound of Formula (A):

\[
\begin{array}{c}
\text{R}^1 \\
\text{L} \\
\text{N} \\
\text{N} \\
\text{HN} \\
\text{R}^2 \\
\text{A} \\
(R^3)_n
\end{array}
\]

Formula (A)

with a compound of Formula (B):

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \\
\text{N} \\
\text{NH}
\end{array}
\]

Formula (B);

and thereafter if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a pharmaceutically acceptable salt, wherein \( L \) is a leaving group.
11. A process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, said process comprising reacting a compound of Formula (C):

\[
\begin{align*}
\text{Formula (C)} \\
\text{with a compound of Formula (D):}
\end{align*}
\]

\[
\begin{align*}
\text{Formula (D)}
\end{align*}
\]

and thereafter if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a pharmaceutically acceptable salt,

wherein \( L \) is a leaving group.